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THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

DECEMBER, 1930

ORIGINAL ARTICLES.

ROENTGENOLOGY OF THE THYMUS IN INFANCY AND DIFFERENTIAL DIAGNOSES OF ENLARGED THYMUS AND ITS TREATMENT.

By Henry K. Pancoast, M.D.,

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Roentgenology of the thymic gland in infancy has received very wide attention since Lange[1] in 1911 published the report of his studies from the standpoint of treatment of the condition of enlarged thymus. The subject has been discussed so generally in literature and there exist so many conflicting views in regard to the cause of thymic death and the potential dangers of the structure in question that one hesitates to introduce any ideas that may be empirical. Notwithstanding the wide discussion, there seems to be very little positive or exact knowledge concerning the potential dangers of thymic enlargement, from either the roentgenologic or other view points, that will warrant anyone in dogmatically agreeing with any single theory. Personally, however, we believe that we have ample justification in basing our own conclusions upon phenomena that can be directly observed during life in a large number of individuals presenting clinical evidences of thymic enlargement and upper respiratory tract obstruction. This being the case, we have concluded that the study of the thymus in infancy, where it assumes relatively large proportions, should be approached through observations of the upper respiratory passages.

The vigorous controversy regarding the exact cause of death in cases of supposed status lymphaticus or enlarged thymus has been waged for well nigh a century. The so-called thymic death has been ascribed to a wide variety of causes. Recently these have been conveniently abstracted and summarized by Marine (1928).[2] The one theory which seems to be most popular at the present time regards the calamity or potential danger as due to the pressure of an enlarged thymus upon the trachea, bloodvessels or nerve trunks. (Kopp,[3] Jackson[4, 5, 6] and Noback.[8]) A second theory ascribes death to a constitutional defect manifesting itself through an injurious raising of the vagus tone, together with a deficiency of the chromaffin system and weakness of the sympathetic system. (Paltauf,[9] Wiesel[10]). Another cause of death that has been stressed is a hypersusceptibility to physical and chemical agents. (Kundrat,[11] Blake.[12]) A fourth theory is anaphylaxis. (Symmers.[13]) Finally, a fifth ascribes death to an abnormal thymic secretion of a general lymphotoxemia. (Svehla,[14] Escherich.[15])

Personally, as previously stated elsewhere,[16, 17] we have followed the trend of most roentgenologists and pediatrists who have seen the wisdom of being on the safe side in the thymic controversy and of recognizing the condition of enlarged thymus as an entity. Our views have been further greatly strengthened by the observations and the statements of Jackson.[4, 5, 6] We believe, therefore, that the potential danger in the infantile thymus lies in its ability to enlarge further and to compress the trachea and the recurrent laryngeal nerves, and to cause other phenomena due to respiratory obstruction. We have observed all of these occurrences roentgenographically and fluoroscopically in the living infant and we have the statements of Jackson upon observations made directly in the respiratory passages during life. Our beliefs and our remarks do not in any way apply to the cause of supposed thymic deaths in adults. We do not believe that compression is a possible cause of death during adult life.

Jackson,[4] in 1907, made the following statement: "It has been my privilege, with the aid of the bronchoscope, to demonstrate beyond all doubt on the living patient the purely mechanical nature of thymic asthma in one instance. This, of course, does not prove that every case has this same pathological mechanism, but it does prove the occurrence of that which many . . . have denied, namely, that a hypertrophic thymus can compress the trachea sufficiently to obliterate its lumen . . . it would seem more accurate to call it thymic tracheostenosis." He further suggested: "Let thymic asthma be applied to cases supposed to be associated with neuropathic, convulsive, lymphatic, rachitic, hemic or other pathology, if desired, until their exact pathological mechanism shall have been demonstrated." Jackson,[5] in 1915, made the following statement, based upon further observations: "Thymic deaths

under anesthesia attributed to 'status lymphaticus' and 'hyperthymization of the blood' are nothing more or less than arrested respiration due to obstructive pressure of the engorged thymus. Artificial respiration is useless, as air cannot be drawn into the lungs, although it can be forced out. After death the engorgement factor is not evident." In a recent personal communication, Jackson[6] stated that "over 300 cases since that time have been observed bronchoscopically, showing compression and the purely mechanical character of wheezing, dyspnea and the impending asphyxia from thymic pressure." "The upper orifice of the thorax is a rigid ring, and coughing, choking and hard breathing jam the large thymus into this ring and compress the trachea. After asphyxia the thymus shrinks because engorgement is depleted, and at autopsy the thymus is no longer compressing the trachea."

Further substantiation of our belief in the compression theory is to be found in the anatomic studies of Noback.[8] According to his investigations, the thymic gland is usually cervicothoracic in location and it is wedge-shaped, with the base below and the apex above. (Figs. 7 and 8.) The apex of the wedge passes upward and through the thoracic inlet in 80 per cent of cases. He believes that the broad type of gland described as typical of the newborn soon becomes molded after the establishment of respiration by the expanding lungs into a more elongated mass. A thymus that is not broad may become thick and press on structures behind it. Our roentgenologic studies made during the two phases of respiration have proven that the thymus is pushed upward during expiration, and it is easy to understand how the apex of the wedge jams up into the narrow, rigid, bony thoracic inlet and compresses other yielding structures such as the trachea, vessels and recurrent laryngeal nerves. (Figs. 7 and 8.)

In view of these observations of an eye witness of actual conditions during life, of the postmortem findings of the character of the gland which readily lends itself to causing pressure, and the confirmation of both by roentgenologic studies, we, who have almost an equal opportunity to confirm these findings in the living, and under circumstances intentionally made conducive to engorgement of the gland, cannot do otherwise than take the stand that the danger in the thymus lies in the possibility of its causing pressure stenoses under certain circumstances. Even it if cannot be proven that actual death results from thymic compression, we have sufficient evidence to lead us to believe that obstructive phenomena and cyanosis can result. It may be that another factor is essential in the causation of asphyxia and death. We know from experience that at least one such factor is possible, namely, recurrent laryngeal paralysis, which is a complication of thymic enlargement, to be discussed later.

Every roentgenologic investigation of the respiratory tract in

infancy and early childhood for any purpose should include a collective study of the nasopharynx, oropharynx, the neck and the chest. Thymic cases are obviously referred for examination because of obstructive symptoms, and experience has taught us that obstructions anywhere in the upper passages may produce phenomena simulating those due to thymic enlargement. A differential diagnosis is imperative and must be made when any condition other than thymus may be present. Many times patients have been referred for thymic examinations, and if a thorough search had not been made, obstructive conditions equally as serious, or even more so, would have been overlooked, such as retropharyngeal abscess, foreign bodies or diphtheritic stenosis. Many suspected intrathoracic conditions besides thymic enlargement may be explained entirely or in part by obstructive lesions or phenomena higher up. At a recent examination of a baby, a suspected tracheobronchitis was confirmed, but our wide anatomic inclusion revealed the presence of a button in the nasal passage on one side. This unsuspected foreign body was no doubt indirectly responsible for some of the symptomatology. During infancy, one never knows what condition may be encountered, and as long as we have a technique for wide inclusion applicable to all, it is the one of choice.

In the detection of conditions in the upper portion of the tract, or upper air passages, down to the bifurcation of the trachea, the basis for diagnosis is the fact that these passages consist of a more or less rigid, air-containing tube surrounded by soft tissues, and lying close to the rigid vertebral column. The lumen of the passage throughout can be visibly encroached upon or displaced by extrinsic or intrinsic lesions. The dense vertebral bodies occupy a fixed relative position for the determination of displacements or making comparative measurements of the various portions of the tract and their locations. Moreover, the spine is rigid and will not yield to extrinsic lesions, therefore they must displace or compress the yielding open tube.

Accurate studies of the chest and upper respiratory tract of infants and young children must be based upon two very important problems—a uniform and comprehensive technique capable of exact reproduction in every instance and the establishment of a normal for different ages.

Roentgenographic Technique.—In infancy and early childhood when the thymus and foreign bodies play such an important part in diagnosis and almost any condition must be looked for we have made our technique adaptable for all examinations. It is the one rather generally in use, with certain slight modifications. A preliminary fluoroscopic study is always imperative. It must be made in the horizontal position because of the age period, and in essentially the same horizontal positions as for the roentgenographic views if the latter are to be made with the patients placed horizontally. At any rate, the patients must be fluoroscoped in both the sagittal and lateral directions. The neck must be included with the chest. The

observer's eyes must be well accommodated before beginning fluoroscopy, and in emergency cases one must wait until the proper time arrives for perfect vision. The child should be crying in a regular manner, or at least, deductions must be based upon such crying, and not on sobbing or irregular or jerky respirations. One looks, of course, for any obvious intrathoracic lesions. The movements of the diaphragm domes must be carefully observed and the relations of the mediastinal shadows to these and any abnormalities at the two phases of respiration carefully noted. One should carefully observe the appearances of the pharynx, larynx and trachea and their relations, expecially during the two respiratory phases.

Roentgenographic exposures may be made according to either a horizontal or a vertical technique or both. In our horizontal technique the patient is placed upon a rather low table with the tube target raised 38 inches above the cassette. For the sagittal views, the infant is placed prone, with its chest and neck upon the casette. The tube target should be directly above the level of the suprasternal notch. One attendant holds the hips and lower extremities flat and a second holds the upper extremities *above the head.* The head must be held exactly straight, midway between flexion and extension and without the slightest rotation to either side. One exposure must be made during inspiration and one during expiration, every effort being directed toward getting them at the peak of each phase. The child must be forced to cry because of the greater accuracy in timing the phases and the deeper respiratory effort. It must be crying lustily and regularly because of the greater accuracy of the effects of such respiratory efforts. Sobbing or "catchy" crying not only makes it more difficult to select the exact phases necessary and at their peaks, but typical respiratory changes in appearance will not be shown. The expiratory exposure should not be made at the end of a long breath-holding period. The exposures must, of necessity, be rapid, not over one-twentieth to one-fifteenth of a second, an appropriate milliamperage being used to make this time exposure correct. The patient is next placed on one side or the other. The arms are held *downward and backward* so that the shoulders are thrown posteriorly as far as possible, in order to clear the neck and upper portion of the chest entirely. The head should be held separately and so elevated that the neck will be absolutely straight with the body and exactly midway between flexion and extension. An exact lateral view of both chest and neck are essential. One exposure should be made at complete expiration and another at the peak of inspiration. Important conditions may be overlooked unless these two lateral exposures are made. The exposure time is approximately twice that for the sagittal views.

For our erect technique we have employed a combination chair and cassette holder which is a modification of the encephalogram chair previously described.[16, 17, 18] An attendant must hold the arms and head of the child. A single attendant is necessary in this technique whereas two or three are required for the horizontal method. The baby sits on a board seat extending across the two arms of the chair. As babies must be held by hand for both methods as well as during fluoroscopy, it is not wise to have any regular members of the staff serve in this capacity. The distance and other exposure factors are the same in the erect as in the horizontal technique.

In the erect sagittal position the arms are held up on either side of the head. The body is held symmetrically so that the sternal ends of the clavicles will appear equidistant from the spine in the roentgenograms and the trachea in the midline. In the lateral views the head must not be allowed to fall to either side and it must be held midway between flexion and extension. The arms are held downward and backward just as in the horizontal technique. One must be careful to keep the child erect and not

permit it to slouch down, for by so doing the large liver in infancy pushes up the domes of the diaphragm and causes buckling of the treachea or increases that which may already be present.

After examining a large number of normal babies and those referred for various pathologic conditions in both the horizontal and erect positions we first concluded that all examinations should, when possible, be made in both positions.[16, 17] This has been advised by Remer and Belden.[19] We soon learned that better roentgenograms could be made and with greater ease in the erect posture, but as the infant usually spends most of its time on its back or abdomen we continued to make exposures in the horizontal position also, in order to obtain as nearly as possible a true idea of the usual postural anatomic relations. Jackson,[4] however, states that the dyspnea in thymic tracheostenosis is worse in the sitting position. Notwithstanding this, the natural tendency of most of us is to raise the horizontally placed child into the erect posture if it becomes dyspneic. What we probably do is to relieve the infant by extending the head and straightening the trachea.

Experience in examining a large number of infants by both methods has taught us that the erect-posture technique is perfectly satisfactory alone and has advantages over the horizontal position. Not only can better roentgenograms be made and with greater ease and fewer attendants in the erect posture, but also the lung fields are more extensive because of the lower diaphragm domes, and in the lateral views these structures are shown at their proper levels and not with the one on the down side elevated as is the case when the child is lying on its side.

We believe that it is absolutely essential to examine all thymic suspects during the two phases of respiration. In the sagittal direction there is a great difference in the width of the shadow of the gland, it being as a rule wider during the expiratory phase (Figs. 1 and 2), and sometimes very much wider. If any comparative measurements are to be made we must have roentgenograms of each phase for the purpose. As a matter of fact, however, we pay but little or no attention to the width of the shadow. The sagittal roentgenograms are of value mainly, as far as the thymus is concerned, to determine thickness or density of the shadow, suggestive of lobation, or lateral deviation of the trachea (Fig. 5). The gland does not obstruct because it is wide, but because it is thick or dense, and this seems to be a rather difficult fact for most examiners to comprehend. Jackson[6] has stated that lateral compression of the trachea occurs in only about 25 per cent of cases, and we must judge this possibility not by the width of the shadow, but by its density, denoting thickness and possible lobulation or the lateral deviation of the trachea (Fig. 5).

In the lateral views, observation of the two phases is necessary in so far as the thymus is concerned, in order to determine compres-

sion or buckling of the trachea at the thoracic inlet, the amount of collapse during expiration and the exact effect produced by the upward push of the wedge-shaped gland into the inlet (Figs. 3, 4 and 7, 8). Moreover, the lateral view of the neck will show different phenomena in the cervical portion of the upper respiratory tract during the two phases.

Another important reason is to be found in the fact that the thymus may not be responsible for obstructive phenomena, and the two phases are quite essential for the detection of other causes of obstruction which may be detected by this complete method of examination. Moreover, the thymus, by itself, is probably not the only cause of obstructive clinical phenomena as a rule. There is usually some additional and associated cause, as collapse of the soft tissues higher up or recurrent paralysis, both of which will be referred to later. In infancy the thymus is a preponderant structure, and when obstructive symptoms are present it usually comes under suspicion at once, unless there is strong presumptive evidence of foreign body, retropharyngeal abscess, diphtheria, whooping cough or a few other conditions, and either it or any of the other possible causes of respiratory obstruction must be proven or excluded by the examination.

Most of us have been under the impression that cyanosis, which if often associated with thymic enlargement, is another evidence of respiratory obstruction. This is not necessarily the case, although we have no way of determining just how often it is or is not. Noback[8] has called attention to the close anatomic relations between the thymus and important bloodvessels. It is closely applied to the superior vena cava on the right side and to the left innominate vein, and sometimes the superior vena cava may be embedded in the posterior aspect of the gland. In several instances Noback noted evidences of compression of the innominate vessels as they passed through the thoracic inlet. One might consider it possible for cerebral disturbances as well as cyanosis to result from interference with the venous return from the neck. In cases of enlargement of the left lobe, the left pulmonary vessels might be pressed upon and cause a general cyanosis which could be mistaken for the result of a congenital heart condition. We have encountered 2 cases in which both a congenital heart condition and an enlarged thymus were present, and it was only through the greatest care in interpreting our roentgenograms that we were able to determine just when the thymus could be permitted to rest from treatment.

Our ability to diagnose an enlargement of the thymus must be based upon a comprehensive study of the normal. In our determination of normal thymic appearances, we examined 78 presumably normal infants during the first year. All were examined at the ages of two and twelve days, and several at six months. Much of our knowledge of the normal neck or upper respiratory tract was estab-

lished through the collective studies made by Hay.[20] To these studies have been added careful fluoroscopic observations of all infants examined for any condition suspected anywhere in the respiratory tract.

A great part of our information in regard to abnormal conditions of the upper respiratory tract depends upon encroachment upon the lumen of or displacement of the pharynx, larynx and trachea. Such deformities or abnormalities of the upper air passages must be estimated by decreased lumen or by changes in the space between their posterior walls and the anterior surfaces of the bodies of the cervical vertebræ. This space and the lumen will vary normally with age, degree of flexion of the neck and the phase of respiration. The phase of respiration has the most marked effect upon the lumen of the pharynx, to be referred to more in detail later. The rigid cartilaginous structure of the larynx prevents changes in its lumen except the ventricles, under normal conditions. The lumen of the trachea changes decidedly. During the expiratory phase and just as inspiration begins, there is a normal collapse of the trachea posteriorly, due to the absence of the cartilaginous ring structure in this aspect. Jackson[6] states that the tracheal collapse in infants is as easy as that of the bulb of a medicine dropper and that the normal change in lumen just at the beginning of inspiration is about 50 per cent, but involves only the posterior or purely membranous portion. By bronchoscopic observation the lumen is seen to become crescentic instead of rounded with the hollow of the crescent posterior. Air remains in the horns of the crescentic lumen and the apparent collapse, as observed in roentgenograms, is, for this reason, not nearly as much as the actual amount. It will be noted, however, that during the period of collapse the posterior aspect of the intrathoracic portion of the trachea is blurred, and not clean cut as compared to the anterior aspect. This is because there is air in only the horns of the crescent posteriorly.

It is always necessary to determine whether or not the space between the trachea or the pharynx and the vertebral bodies is normal or widened. Hay[20] has proposed an admirable method for making comparative measurements of this space by using the sagittal width of the ossified portion of the body of the fifth cervical vertebra as the index of measurement. This vertebral width he arbitrarily designates as "C." With the pharynx at rest the distance between its posterior surface and the osseous portion of the adjacent vertebræ measures at the level of the epiglottic vallecula approximately as follows: First year, never over 1.5 C; first to third year, never over 0.5 C; third to sixth years, never over 0.4 C; sixth to fourteenth years, never over 0.3 C. In adults the *average* measurement is as follows: Males, 0.2 C; females 0.1 C. These measurements of the retropharyngeal space in infants were made with the pharynx at rest and not during crying. They will vary with crying. As our

present technique includes lateral roentgenograms during both phases of respiration, additional measurements are required for the two phases. These we have not yet completed in connection with our normal cases. Measurements have also been established by Hay[20] for the retrotracheal space. As this space does not concern us so much in infancy and early childhood as in adult life, with the exception of the effects of foreign bodies, there is no necessity for giving any of the details here.

In the complete study of the upper respiratory tract, and especially for purposes of differential diagnosis, it is important to observe, either by fluoroscope or roentgenogram or by both, many landmarks bounding the air passages in the neck. In the infant and young child the shadows of the following structures should be more or less clearly shown:

1. The pharynx. This air space has been freely discussed and is always easily recognized. It is continuous with the oropharynx and nasopharynx above, and narrows below as it reaches the vestibule of the larynx and pyriform sinuses.
2. The posterior border of the tongue (Fig. 3) curving down to the base of the epiglottis.
3. The uvula and soft palate (Fig. 4).
4. The epiglottis (Fig. 3) is seen in all satisfactory roentgenograms.
5. The arytenoid cartilages (Fig. 3) are also always visible.
6. The superimposed aryepiglottic folds can often be observed.
7. The superimposed pyriform sinuses (Fig. 3).
8. The vestibule of the larynx is readily located by its boundaries. Its base is the upper border of the ventricular folds. Its anterior boundary is from the base of the epiglottis to the ventricular folds. Posteriorly one sees the arytenoids.
9. The ventricular folds are often demonstrable in the infant. They are always seen in the normal adult under proper exposure.
10. The vocal cords often can be seen.
11. The laryngeal ventricles, when seen, easily determine the ventricular bands and the vocal cords.
12. The trachea begins at approximately the lower border of the cricoid cartilage. The latter is likely to superimpose the vocal cords and often cannot be differentiated in infancy.

THE ROENTGENOLOGIC SIGNS OF ENLARGED THYMUS IN INFANCY OR POTENTIAL ENLARGEMENT may be summarized as follows:

1. Lateral deviation of the trachea, established by the sagittal view (Fig. 5).
2. Narrowing of the trachea at the thoracic inlet during inspiration, and determined by the lateral view (Figs. 3, 4 and 7).
3. More than the normal amount of collapse at the thoracic inlet at the expiratory phase (Figs. 3, 4 and 8).

4. Buckling of the trachea at the thoracic inlet at either phase. This must be based upon a rigidly enforced technique, especially in connection with the position of the head. Flexion is likely to produce an appearance simulating buckling.

If the child is not crying regularly, but is sobbing, a marked collapse of the entire trachea may be produced during the expiratory phase just as inspiration is about to begin, whether the thymus is enlarged or not, whereas the true thymic effect is observed only at the thoracic inlet. This likelihood of error from the improper type of crying has been demonstrated by fluoroscopic studies.

The examination for enlarged thymus as it has been carried out ordinarily in the past does not, we believe, show the *exact* evidences of abnormal enlargement.

Complicating Factors in Obstruction. Our observations have led us to believe that the enlargement of the thymus *per se* and the resulting tracheal compression may not be the only cause of obstruction and the attending phenomena, especially in the more severe cases. There are two additional factors to which little attention has been paid, but when we analyze them and their possibilities we can readily realize their importance. The first is the collapse of the soft tissues of the upper respiratory tract—a contributing factor, and recurrent laryngeal paralysis—a result of the hypertrophy of the gland. Atelectasis and drowned lung must be regarded as more or less a result of thymic tracheostenosis and a complicating factor in the clinical phenomena.

Collapse of Soft Tissues. In infancy and early childhood there is an unusual degree of relaxation of the soft tissues of the pharynx, larynx and aryepiglottic folds. In the adult, the retropharyngeal tissues are relatively thin and closely attached to the vertebræ, whereas in the very young these tissues are very loosely attached. This is one of the important factors in the frequency of retropharyngeal abscess from lymphatic extension of infection in infancy. This looseness of soft structures is quite evident in connection with the aryepiglottic folds and the ventricular and vocal bands in the larynx.

If the pharynx of an infant is studied fluoroscopically and by carefully timed roentgenograms it will be found that its appearance differs very greatly during the two phases of respiration. The pharyngeal lumen is much wider and the retropharyngeal space much narrower during the inspiratory phase, whereas the lumen narrows considerably and the retropharyngeal space widens during expiration, especially just before inspiration begins. These phenomena will not be accurately shown unless the infant is crying lustily and regularly (Figs. 3 and 4). They are evidences of the looseness of soft tissues and these expiratory phenomena demonstrate the tendency of collapse in infancy. The degree of collapse gradually diminishes up to about the third year, after which it is negligible and not noticeable. The finding of the two distinct

appearances on roentgenograms often serves as proof of accurate timing of the inspiratory and expiratory exposures.

In the necks of many infants we have noticed that the shadow of the tips of the arytenoid cartilages closely approximate the lower margin of the epiglottis, especially at the very end of expiration, as the inspiratory phase is about to begin (Fig. 3). This is the position assumed normally during the swallowing act, except that the epiglottis drops slightly to meet the arytenoids, which are carried upward by an elevation of the larynx. The appearance in infancy during respiration was at first regarded as an evidence of unusual soft-tissue relaxation and resulting collapse, but as it was later noted in many clinically normal infants (Figs. 3 and 4), we have learned to regard it as abnormal and as an evidence of collapse only when there is an associated lack of air in the laryngeal vestibule. This combination has been noticed quite frequently in some cases of enlarged thymus.

While unusual relaxation of soft tissues does not in itself cause any definite obstruction to breathing, still, it seems possible that under the stress of obstruction elsewhere in the upper respiratory tract, these structures tend to collapse and this undoubtedly becomes an intensifying factor in the obstruction. Jackson[6] states that the collapse of loose tissues may aid in the obstruction in any case in which the child has to pull hard just at the beginning of inspiration. Further than this, unusual relaxation of soft tissues does no harm. Sometimes it will produce a peculiar respiratory noise which has often been mistaken clinically for an evidence of thymic obstruction in cases in which we have been unable to find any evidences of abnormal enlargement of the gland. According to Jackson, unusual relaxation and collapse are seen most frequently in association with rickets.

Recurrent Laryngeal Paralysis. We have studied 3 cases in which paralysis of the recurrent laryngeal nerves was a complication of enlarged thymus. These are practically the only nerves which are likely to receive serious pressure as they pass through the thoracic inlet. Boyd[21] has called attention to the possibilities of this complication from the standpoint of anatomic studies. Based upon clinical observations, she has also suggested that the frequent inspiratory stridor, hoarseness or crowing cry may be due to spasm of the vocal cords from irritation of the recurrent laryngeal nerves. Certainly, if a goiter in the neck, where there are no bony confines, can cause recurrent paralysis, it is easy to understand how much more readily the apex of the thymic wedge jamming up into the bony ring of the thoracic inlet can produce paralysis of these nerves. In our cases, confirmed by endoscopy, either the right or left cord has been paralyzed. Therefore, as either nerve may be involved it is quite possible that both can be.

According to Jackson,[6] bilateral paralysis is rapidly fatal unless

immediate tracheotomy is performed. He has had to operate three times for bilateral involvement, but never for unilateral involvement. He has observed no bilateral cases since the advent of Roentgen therapy. We are inclined to believe that this condition or complication may have been responsible for at least some of the thymic deaths in infancy. Jackson[6] states that recurrent laryngeal paralysis is more serious in infants than in adults because of the loose structure of the laryngeal and pharyngeal tissues which aid in the obstruction in the very young.

Recurrent laryngeal paralysis usually persists for some time after the gland has been reduced to a safe size by appropriate treatment. A persistence of symptoms is then not due to thymic pressure, but the fact that symptoms persist should act as a warning to consider endoscopy unless they can be explained in a satisfactory manner. Recurrent paralysis is elusive to the roentgenologist because he cannot detect it, although he may sometimes suspect it through failure to demonstrate the ventricles of the larynx or because of suspicious but indefinite signs of high obstruction without adequate explanation. He should always have the possibility of the complication in mind.

Atelectasis and Drowned Lung. Enlargement of the thymus is likely to be present at or soon after birth. It interferes with proper aëration of the lungs. Chilling of the infant may cause further engorgement of the gland and the outpouring of secretion which cannot readily escape. Atelectasis may result from either lack of aëration or retained secretions. It may involve extensive or small areas. If widespread, there is likely to be the classical mediastinal shift to aid in the diagnosis. The so-called drowned lung from retained secretion will closely resemble atelectasis, especially on the expiratory phase, although its nature is likely to be indicated in the inspiratory phase roentgenogram. Both of these conditions will clear up sooner or later after reduction in the size of the thymus.

Differential Diagnosis. Attention has been previously called to the fact that high respiratory obstruction may be due to many other causes than enlarged thymus, and our method of examination must include every other possible cause of obstructive phenomena. We are often too prone to be misled by the relative preponderance of the infantile thymus and to overlook other possibilities. Moreover, the physician who has had the unfortunate experience of observing cases of thymic death may be too hasty in ascribing obstructive phenomena to the thymus when they are due to other causes. Our experience has taught us that this is quite a frequent attitude on the part of many physicians. Many of the conditions that have been misleading are most surprising. Under the circumstances of personal experience we are obliged to list the following conditions as necessary for discussion under differential diagnosis: Foreign

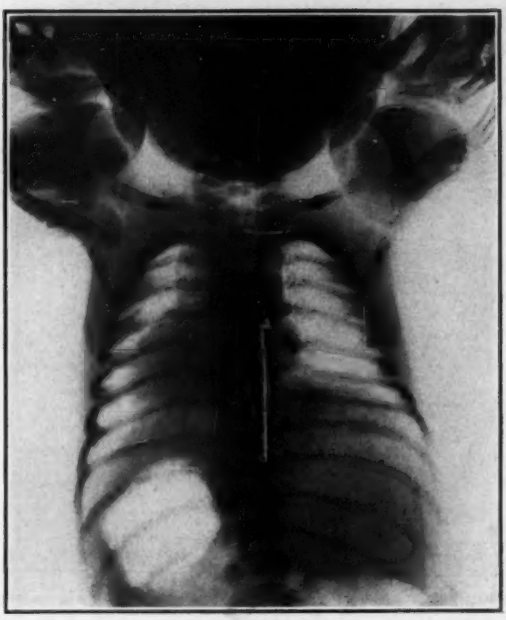

FIG. 1.—Normal thymus. Sagittal view of infant a few days old; expiratory phase, horizontal technique. Note the width of the thymic shadow. This is of no significance in diagnosis. The trachea is not deviated laterally.

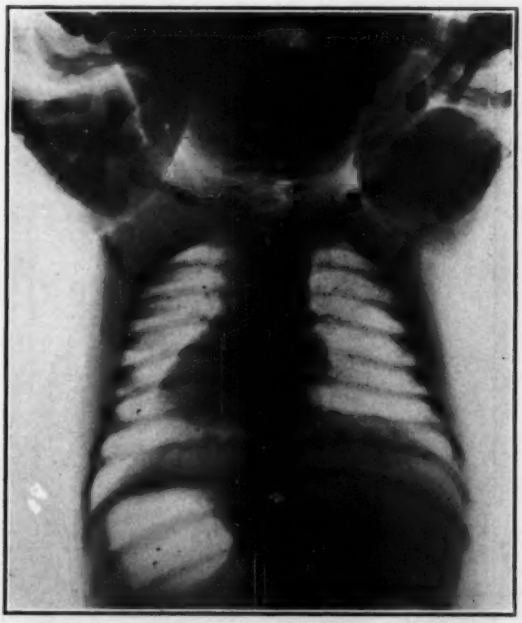

FIG. 2.—Sagittal view of the same case as Fig. 1; inspiratory phase. Note the decreased width of the thymic shadow.

FIG. 3.—Lateral view of the same case as Figs. 1 and 2; expiratory phase. The arrow points to the trachea at the thoracic inlet. There is no buckling and no unusual narrowing of the lumen. *A*, pharynx (the fact that it is wide open during this phase indicates that the child was not crying properly or that this was not the point of full expiration); *B*, epiglottis; *C*, vestibule of the larynx. The vertical shadow behind this is that of the arytenoid cartilages.

FIG. 4.—Lateral view of the same case as Figs. 1, 2 and 3; inspiratory phase. There is no buckling or narrowing of the trachea and, therefore, no thymic enlargement of an obstructive character in this case.

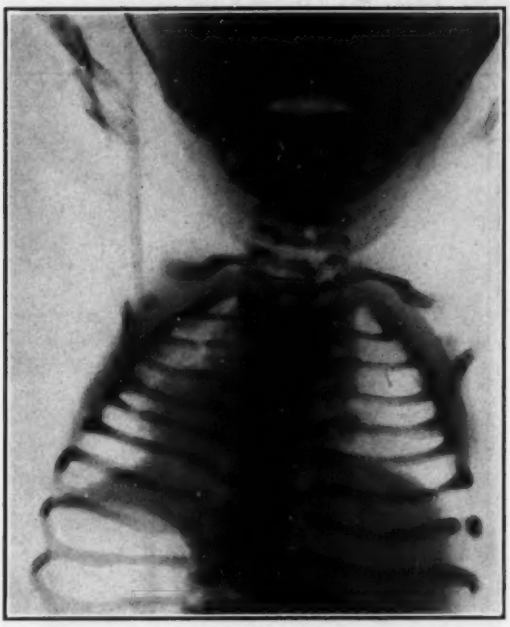

FIG. 5.—Enlarged thymus in an infant, aged three weeks, indicated by a lateral deviation of the trachea during the expiratory phase. During the inspiratory phase it was almost in the midline. The lateral views showed buckling of the trachea at the thoracic inlet and too much narrowing on expiratory phase.

FIG. 6.—Retropharyngeal abscess in a child aged seven months. (Referred by Dr. Tucker.) Note the wide retropharyngeal soft tissue space.

FIGS. 7 to 10.—Roentgenograms of an infant with clinical and roentgenologic evidences of enlarged thymus and upper respiratory tract obstruction and atelectasis of the right lung. Figs. 7 and 8 represent the condition of the chest and upper tract two days after premature delivery at eight months and five hours before treatment. Figs. 9 and 10 show the appearance seventeen hours after treatment.

FIG. 7.—Lateral view, horizontal posture, inspiratory phase. There is marked narrowing of the trachea as it passes through the thoracic inlet behind the apex of the thymus. This should not occur during this phase. The apex of the gland can be seen in this and the next figure.

FIG. 8.—Lateral view, expiratory phase. There is a little more than normal amount of tracheal collapse at the thoracic inlet.

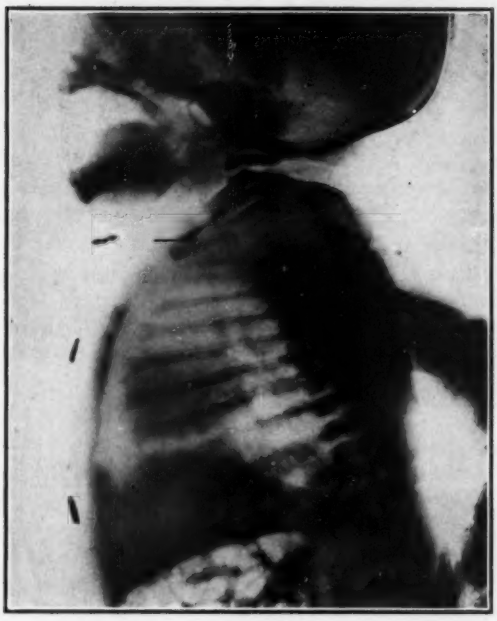

FIG. 9.—Lateral view, inspiratory phase. Note how much wider and straighter is the trachea.

FIG. 10.—Lateral view, expiratory phase. This shows about the normal amount of tracheal collapse during this phase.

bodies, retropharyngeal abscess, tracheal and laryngeal stenoses, adenoids, asthma, whooping cough, meningitis, congenital heart conditions, congenital atelectasis, collapse of soft tissues and recurrent laryngeal paralysis. The last three have already been discussed in detail.

Foreign Bodies. One cannot always depend upon a history of foreign-body inspiration in infancy, and especially those belonging to the nonopaque group. Opaque bodies should, of course, be very readily detected even aside from the obstructive phenomena they may produce. The detection of nonopaque bodies depends entirely upon the study of the obstructive respiratory phenomena they induce. Foreign bodies in the trachea produce signs of expiratory obstruction as a rule. Those below the bifurcation cause atelectasis, drowned lung or obstructive emphysema in the distribution of the bronchus affected.

Retropharyngeal Abscess. As retropharyngeal and retrotracheal or retroesophageal abscesses will cause encroachment upon the air passages they may produce phenomena of high respiratory obstruction which have quite frequently, in our experience, been mistaken clinically for those due to enlarged thymus. We have seen cases in which the preponderant thymus of infancy has even thrown the roentgenologist off the track and caused him to overlook an abscess responsible for the symptoms and to regard the thymus as the cause, whereas it was not abnormally large according to our estimations. The diagnosis of abscess is very easy if the technique advised is rigidly carried out and the condition may often be detected roentgenologically before it is suspected clinically. The diagnostic sign is a decided increase in the retropharyngeal or retrotracheal space (Fig. 6). The larger dimension of the retropharyngeal space during the expiratory phase in infancy may be confusing, but the narrowing during inspiration should correct any misapprehension. In the abscess case this narrowing does not occur. In the series of abscess cases reported by Hay[20] from our department the retropharyngeal space measured one and a half to ten times the normal for the age of the individual. Unilateral abscess may be difficult to detect, but we were able to make a diagnosis in one such case.

Case Report.—In this connection it is worth while calling attention to a case recently examined by us in which the retropharyngeal space was twice that of the normal for the infant. The case was a cretin, aged four months, referred because of difficulty in breathing and dysphagia and a suspected thymic enlargement. There was no evidence of obstruction from the thymus. Because of the increased retropharyngeal space shown by the lateral view a diagnosis of abscess was made. Endoscopic examination revealed a normal mucosa without swelling but did show that the enormous tongue of the cretin was responsible for the respiratory and swallowing difficulty, partly because of its size and partly because it pushed the larynx downward and backward. A review of our lateral roentgenograms showed that this was the case, and that the downward and backward displacement of the

larynx widened the retropharyngeal space. A contributing factor of more or less importance would be the thickened neck tissues of such a patient. This case is mentioned because of the difficulties in diagnosis which anyone may encounter in connection with an infant cretin.

Retropharyngeal or retrotracheal abscess may occur at any age but varies as to causes and location at different age periods. In infancy and early childhood the most frequent cause is lymphatic extension of infections from all sources which may cause infections of cervical lymph nodes. There is a very free lymphatic communication to the loose retropharyngeal tissues, and lymph nodes are found even in this locality during early life. In the adult, on the other hand, the perforation by lodged sharp foreign, bodies such as fish bones, swallowed with food is the common cause, and for this reason, the abscess is usually retrotracheal or retroesophageal rather than retropharyngeal. Even though perforating foreign bodies such as pins, safety pins, jackstones and collar buttons are well recognized causes in children, they are relatively infrequent factors as compared with infections. It is, of course, necessary to exclude a large non-opaque foreign body in the esophagus, such as a piece of potato or bolus of meat, as the cause of a retrotracheal swelling, and also a growth in an adult.

We have been able to diagnose abscess in 26 cases since roentgenology has been used for this purpose. Sixteen of the patients were children and 10 adults. In not a single instance was tuberculous caries of the spine found as a cause, although in 2 adult cases an accompanying osteomyelitis of the vertebræ resulting from gunshot injury was detected.

Stenoses of the Trachea or Larynx. Included in this group of obstructions are streptococcic infection of the larynx, acute diphtheritic infections, postdiphtheritic stenosis, scars as from tracheotomy wounds and congenital stenoses. Streptococcic infections of the larynx may cause considerable obstruction to respiration because of the narrowing of the lumen of this portion of the passage. The lateral view of the neck will show a decided narrowing of the lumen and absence of the ventricles. The arytenoids are likely to be swollen. This appearance can hardly be differentiated from the effect of acute diphtheria.

We have encountered one case of acute laryngeal diphtheritic infection in the larynx. The condition was not diagnosed by us at the time, but the fluoroscopic and roentgenographic appearances denoting high obstruction for which no cause could be found called for an immediate endoscopic examination and Dr. Tucker found the condition in the larynx. At the present time we should be able to detect practically any severe inflammatory process in this structure.

The postdiphtheritic cicatricial stenosis affects particularly the conus elasticus extending from the vocal cords to the first tracheal

ring. The loose tissues in this region, including the cords, are the seat of such intense inflammatory disease as to cause cicatricial contraction afterward, and the cords are usually approximated. In severe cases with perichondritis of the cricoid the larynx is more or less completely obstructed and the upper trachea is also found narrowed considerably or completely stenosed by roentgenologic examination, probably because of the incomplete circumscription by the tracheal rings posteriorly . As pointed out by Hay,[20] this is the main point of distinction between the appearances of post-diphtheritic stenosis and the obstruction caused by acute diphtheritic membrane, which obstructs the narrowest portion of the passage in the region of the vocal cords and immediately below. The inflammatory reaction in acute disease will also narrow the entire laryngeal air space. Postdiphtheritic stenoses are very common and should be readily detected, and if found in a thymic suspect, one must be able to decide as to whether or not the thymus is really encroaching on the trachea and just how much of an obstructive factor exists in the stenosis.

There is no reason why traumatic scars and congenital stenoses should not be easily detected by careful technique.

Adenoids. In one instance a thymic suspect was found to have no enlargement of the gland, but the shadow of a large mass of adenoid tissue was found to almost obliterate the nasopharynx.

It may seem strange that such unusual conditions as are discussed in connection with differential diagnosis should be confused with enlarged thymus, but there seems to be a tendency at present to place the blame for any trivial or serious respiratory abnormality in infancy upon this structure. The gland is often unusually wide to physical examination, and although this is not the real menace of the thymus, this very feature may tend to throw suspicion further upon it. Fortunately it is within the power of the roentgenologist to correct these unusual impressions.

Asthma. Asthmatic cases are apt to be confusing to the roentgenologist for the reason that if the examination is made during an attack the phenomena observed during the two phases of respiration simulate those of high obstruction. While he may not find any evidences of thymic compression or distortion of the trachea, he may not be able to explain the phenomena. The best he can do is to make a negative diagnosis of enlarged thymus.

Whooping Cough. The associated tracheobronchitis and spasm of the glottis in this condition may be confusing at times.

Meningitis. In connection with this condition we can cite one case which has been previously reported[16, 17] and which caused considerable confusion.

Case Report.—A child when seventeen days old was admitted to the hospital as an emergency case because of sudden onset of cyanosis, catchy respiration, occasional twitching of the extremities and, later, general con-

vulsions. It had been sent in as a case of enlarged thymus and this diagnosis was more or less accepted. Careful fluoroscopic and roentgenographic study failed to show any of the signs of thymic enlargement, no evidences of respiratory obstruction and nothing abnormal in connection with the lungs. The child died soon after the examination and a postmortem cisternal puncture proved the presence of a streptococcic meningitis. It is worthwhile considering the possibility of blame upon the treatment had the examination not been made or a negative roentgenologic thymic diagnosis not rendered and the child been treated on the basis of the clinical suspicions.

Congenital Atelectasis. We have become convinced that in some cases of congenital atelectasis the lack of aëration of the lungs may be due to the obstruction offered by an enlarged thymus, and that the nonaërated portions of the lungs may clear up after treatment.

Congenital Heart Conditions. Some of the clinical phenomena arising from congenital heart lesions may be confused with those of enlarged thymus, or both conditions may coëxist. We have had 2 cases in which a congenital heart condition existed, and one of them has many points of interest:

Case Report.—An infant, aged five weeks, was referred for examination for enlarged thymus because of marked cyanosis and some obstruction to breathing. Roentgenograms showed considerable buckling of the posteriorly displaced trachea over the apex of the thymus during the inspiratory phase and there was more than the usual amount of expiratory collapse. A treatment was given on the basis of these findings, although it was not thought likely that the tracheal compression as shown was responsible for all of the cyanosis. Two other possibilities were considered—pressure upon the left pulmonary artery or a congenital heart lesion. The cyanosis was somewhat improved by the treatment but still continued. Another application was made two weeks later and the baby stopped breathing just at the termination and was thought to be dead. Artificial respiration was the only recourse in the emergency and was fortunately successful. Another examination made about two months later showed no tracheal buckling and no unusual collapse. In view of this improvement it was thought probable that the continuance of cyanosis was due to a congenital heart lesion, although this could not be confirmed by roentgenologic study. Eleven days later, a third examination showed a recurrence of the evidences of thymic enlargement and an emergency treatment was given. Over a period of two more months two examinations still showed enlargement and two treatments were administered. The baby died the day following the last treatment.

Autopsy revealed the following conditions: The thymus was very small but the apex *extended well up into the neck* through the thoracic inlet. Evidently the lymphoid structure had been very much reduced by treatment and the continued enlargement was due to the heart condition. When the thymus was removed the thoracic inlet would just admit the index finger, which shows the scant room for all the structures passing through this rigid bony ring. There was a congenital heart lesion consisting of a transposition of the aorta and pulmonary artery and a patulous interventricular septum. The anomaly was not compatible with life.

The baby had considerably more than the usual amount of treatment over a period of five and a half months, although the total application in this time was considerably less than 2 erythema doses. The marked effect

of this upon the lymphoid structure was well shown at autopsy. The apex of the gland was in an unfavorable location and conducive to pressure. The gland, in itself, may not have been too large if the congenital heart condition had not existed, and the latter may have been a decided factor in causing engorgement which would not be affected by treatment. Nevertheless, the reduction in lymphoid tissue by treatment undoubtedly reduced the menace of the engorged gland for a time.

Treatment. We have always felt certain, ever since it was our privilege to discuss the first presentation on the Roentgen treatment of enlarged thymus by Lange[1] in 1911, that the effect of the irradiation was upon the lymphoid tissue of the gland. It was well known to us through our experience in the treatment of leukemia that embryonal types of lymphoid tissue were extremely susceptible to irradiation even with very small doses.

There seems to be some misunderstanding and even skepticism in regard to the rapid effect of irradiation in reducing the size of the thymus. As early as 1905, our irradiation work carried out in conjunction with experimentation by Edsall[26, 27, 28] showed that enormous amounts of waste tissue products were very rapidly liberated by irradiation over the spleen in leukemic cases. Aldrich[22] states that the results obtained from radiotherapy are often too rapid to be explained by a reduction in the size of the thymus. This supposition, we believe, may be refuted by the following case recently treated and most carefully studied because of the important status of the patient:

Case Report.—The infant was prematurely delivered at eight months. For an hour or two it was exposed to cold and there was afterward an unusual outpouring of respiratory-tract secretion and the infant choked considerably. This was followed by attacks of shallow respirations and cyanosis coming on every two or three hours. It was given oxygen and carbon dioxid inhalations each time and improved and then another attack would occur. These phenomena continued for two days and atelectasis was diagnosed and the question of enlarged thymus arose. At this time the prognosis was considered very grave. A Roentgen examination showed marked narrowing of the trachea at the thoracic inlet and drowned lung on the right side (Figs. 7 and 8). The infant was given a Roentgen ray treatment five hours later. After one hour the oxygen and carbon dioxid were no longer necessary, and a second examination made in seventeen hours showed a normally patulous trachea and a disappearance of the drowned lung (Figs. 9 and 10), and the patient had no further respiratory difficulty.

It has been frequently stated that chilling of an infant followed by the outpouring of secretion is likely to be followed in turn by an associated engorgement of the thymus. This may be true, but irradiation of the gland will not reduce engorgement directly. In another case, treated by us, the engorgement factor may have played a part in the fatal outcome. A newborn and cyanotic infant was brought into our clinic on a cold day and an enlarged thymus was

found by examination. The father was keeping up artificial respiration under instructions from the physician. Treatment was given immediately. The father was requested to leave the baby in the hospital to be watched and given oxygen inhalations. He refused to do this and took the infant home again in the cold and it died, even though artificial respiration was continued by the father. It will be explained later that oxygen and carbon dioxid inhalations are far preferable to artificial respiration, which may be even dangerous. This case, by the way, is the only mortality we have experienced in connection with enlarged thymus treatment with the exception of the two congenital heart cases previously and subsequently mentioned. The latter deaths were not results of the thymic condition, however. We have treated 315 cases of enlarged thymus from 1912 up to April, 1930. Of these 271 have been treated since 1924.

The second congenital heart case just referred to is of interest, first, because of the combination of symptoms arising from the cardiac condition and a slightly enlarged thymus which may or may not have resulted directly therefrom, and, second, for the reason that the autopsy showed the decided effect of slight irradiation upon the gland.

Case Report.—The baby, when two months of age, was referred to us by Dr. Gittings for examination for suspected thymic enlargement because of difficult respiration, slight cyanosis and failure to gain in weight. Roentgen examination showed a dense but not wide thymic shadow in the sagittal views, but there was some lateral deviation of the trachea. The lateral views showed slight posterior buckling of the trachea over the apex of the thymus at the thoracic inlet, but no abnormal narrowing. The cardiac shadow was considerably enlarged to the left. An increased density of the right lung with mottling was interpreted as evidence of drowned lung or retained secretion from partial obstruction of the right main or upper lobe bronchus. There was evidence of considerable soft-tissue collapse into the larynx. The infant immediately received approximately one-sixth of an erythema dose of Roentgen rays over the thymic area. Its condition did not improve and a similar dose was administered two days later, making in all not over one-third of an erythema dose at the skin surface. At this time, because of a systolic murmur and the enlargement of the cardiac shadow, a congenital heart lesion was suspected clinically, and we advised against further treatment. Another examination on the sixth day showed the heart shadow to be larger, the thymic shadow somewhat smaller and normal by lateral views and the lung appearance unchanged. The respiratory difficulties continued. The baby died fifteen days after the first examination and treatment. Autopsy revealed the following conditions:

The thymus was quite small, being approximately 2 by 3.5 cm. in size, and evidently could not at this time cause high obstruction unless possibly under the stress of considerable engorgement. There was a patent ductus arteriosus which produced some stenosis of the aorta at the site of the anastomosis. The aortic arterial blood was shunted into a dilated common pulmonary artery coming off from the right ventricle. From this the right and left pulmonary arteries arose. Dilated right ventricle and auricle compressed the right lower lobe bronchus and possibly the main bronchus.

This was a borderline thymus case and the cardiac condition could have caused the very slight enlargement. The lateral tracheal shift was probably a result of the heart condition. The noticeable decrease in the size of the thymus by roentgenologic study was confirmed by autopsy, and showed the effect of a small dose of irradiation. This death occurred just at the completion of this presentation, and microscopic studies of both cases are just available. In both glands there was a decrease in the cellularity of lymphoid structure. Fibrous tissue was concentrated from diminished size of the glands. The epithelial structure was not changed in any way.

As previously stated, we have been led to assume, by the preponderance of evidence at hand that our treatment is directed toward the reduction of excessive lymphoid tissue in a structure that from its location, anatomic relations and its contour is capable of exerting obstructive pressure upon the upper respiratory tract during infancy. The diminution in the amount of lymphoid tissue by irradiation seems sufficient to reduce the size of the gland to a safe limit whereby it no longer can act as a menace to respiration. It is possible that some of the other theories in regard to thymic death or the potential dangers inherent in the thymus may be true or the conditions they represent act as contributing factors and the treatment may have the same desirable ultimate effect brought about in a different manner. Aldrich[22] has recently proposed a very interesting theory in connection with the combination of conditions considered by various authors as status lymphaticus, enlarged thymus and some of the phenomena of vagotonia.

He calls attention to the experimental work leading up to the possible assumption that vagotonia may result from an autonomic imbalance on the basis of suprarenal insufficiency. As the suprarenals of the newborn undergo partial involution during the first two weeks, suprarenal function may be reduced too far in some instances, and if it reaches a sufficiently low point vagotonia may be induced. Suprarenal insufficiency may in addition lessen blood-sugar response to unusual demands and lead to hypertrophy of lymphoid structures, including the thymus.

Aldrich quotes Waldbott[23] as reporting beneficial results in bronchial asthma following irradiation over the spleen. This is, of course, another extensive lymphoid structure. Peterson[24] is quoted as stating that irradiation over any large lymphatic structure may result in an effect antagonistic to the vagus, possibly due to a nonspecific protein reaction resulting therefrom. If, therefore, relief from vagotonia could result from a nonspecific protein reaction following irradiation of lymphoid tissue, the thymus, being one of the large masses of such tissue would be the preferable structure to treat, and would be preferable to the spleen.

If all of these theories should be true; if suprarenal insufficiency

should be a cause of thymic hypertrophy; if vagotonia should be responsible for certain symptoms believed to be associated with enlarged thymus or adding to their complexity and they can be relieved by the elaboration of nonspecific protein; or if, on the other hand, the symptom complex of obstructive breathing can be laid to a purely mechanical factor inherent in a structure undergoing developmental changes in infancy, the treatment remains the same. Vagotonia and its relief by nonspecific protein elaboration through treatment of a lymphoid structure might be used as an explanation of the results obtained in the relief of pylorospasm and of supposed asthma, especially in older children, by irradiation over the thymic area.

Treatment Technique. In the treatment of enlarged thymus we are dealing with a lymphatic structure which is extremely susceptible to irradiation. There is no necessity to apply a larger dose than is absolutely necessary to reduce the gland to a safe size. As long as we do not know the exact effects of the elaboration of tissue products, it is not wise to give more than just enough treatment to accomplish the desired results. Such a dose could not impair any glandular secreting function of the thymus. The exact dose will depend upon the age and size of the child and the thickness of the chest wall. In very early infancy we employ from one-tenth to one-fourth of a mild skin erythema dose with the following factors: 130 K.V., 5 mm. aluminum filter, 9½ inches target skin distance. Only the entire thymic area is exposed. From the fourth month to the end of the first year, from one-third to one-half an erythema dose is employed, depending on the age and size of the child. Most of the patients are young infants and the dosage is small. No treatment is ever given until after we have had the opportunity of making a thorough study of the neck and chest.

After the first treatment, the baby is to be seen by the physician as often as may seem necessary, and if at the end of a week or ten days, there is any persistence of symptoms, a second application is given. If there is any doubt as to the necessity for this, another examination is made. Further treatment may be necessary, but the average number of applications is two, not including recurrences. Recurrences are to be expected in a fairly large percentage of cases, and require treatment.

During all examinations and treatments care should be observed in not permitting infants to become chilled, for reasons that have already been suggested. Parents should be warned to keep the child warm on the way home.

In preparation of the infant for treatment it is securely wrapped in a sheet, but given ample breathing room. With the baby on its back, the sheet is then fastened with large safety pins between each arm and the body and between each lower extremity to the mattress of the table. A canvas band 6 inches broad, with sand bags at each end, is placed across the knees to keep the legs down. A sand bag is placed against each side of the head and another sand-bag band is placed across these to keep the head down. It does not cover more than the forehead, and a folded towel is placed between the band and the skin. An opaque rubber sheet is placed over the entire body below the thymic area. A fenestrated lead shield is placed over the chest, neck and chin so that only the thymic area will be exposed.

If the infant is breathing badly and there is danger of cessation of respiration in a very serious case that is not struggling, we advise against fixation of the restraining sheet to the mattress in order that measures for resuscitation may be inaugurated quickly should occasion arise. The really serious cases are apt to keep quiet without restraint.

During the treatment of all thymus cases the infant should be carefully watched by a physician member of the staff who will be able to act quickly in case of any untoward obstructive manifestations.

The question naturally arises as to the best procedure to follow in case resuscitation measures are required for suspended respiration. The natural inclination of most of us has been to raise the baby into the erect posture. Jackson[4] states, however, that thymic tracheostenosis is worse in the erect posture, and yet all of us have seen respiration begin when the child is raised up. What we probably do under the circumstances is to raise the head up and straighten the trachea and thus relieve a certain amount of buckling over the apex of the thymus. One of our first efforts, therefore, should be to straighten the head and trachea. The next natural inclination would be to practice artificial respiration. In this connection, Jackson[5] further states that artificial respiration is useless in arrested respiration from enlarged thymus because air cannot be drawn into the lungs, although it can be forced out. We have had one experience in which artificial respiration did revive a baby after it stopped breathing (congenital heart case previously referred to). It is possible that engorgement of the thymus may decline to a certain extent after breathing ceases, and artificial respiration may revive the child. Certainly, if it does not do so very quickly, mouth-to-mouth insufflation should be at once adopted as the preferable and safer method of resuscitation.

A very serious thymic case requires very great care after treatment during the period before irradiation takes effect. This is particularly applicable in the newborn, especially when exposed to cold. Such a baby is likely to have atelectasis or drowned lung or both along with the thymic obstruction. It needs oxygen and it requires respiratory stimulation. A mixture of 95 per cent oxygen and 5 per cent carbon dioxid answers the purpose admirably as proposed by Henderson.[25] We have observed 2 cases recently in which the inspiration of such a mixture with the tube outlet at the mouth kept the patients breathing safely until the crisis was passed in a very few hours.

Summary. 1. The stand is taken that the thymic menace in infants and young children is largely a matter of tracheal stenosis, aided by relaxation of the soft tissues of the upper respiratory tract. The complication of recurrent laryngeal paralysis is a most serious one.

2. The diagnosis of thymic enlargement has been based in the past largely upon erroneous roentgenologic evidences. The only definite and reliable signs of an enlarged or potentially dangerous gland are abnormal narrowing or buckling of the trachea at the thoracic inlet as it passes over the apex of the gland, and as shown in only the lateral view of the chest, and lateral deviation of the

trachea as shown by the sagittal view. Unusual width of the gland shadow is of no particular significance, and a gland producing a narrow shadow is likely to possess far more inherent danger than a wide one, as shown by the sagittal roentgenogram.

3. The naturally preponderant gland of infancy may be blamed for obstructive phenomena for which it is in no way responsible. The examiner must adopt such a roentgenologic technique as will enable him to detect any other form of upper respiratory tract obstruction which he may be able to show, such as foreign bodies, both opaque and nonopaque, the effect of obstructive specific laryngeal infections upon the lumen of the larynx, postdiphtheritic and other forms of acquired or congenital stenoses, retropharyngeal or retrotracheal abscess, adenoids, atelectasis and unusual collapse of soft tissues. He must have in mind certain conditions that may confuse the diagnosis, and must call attention to them when no discoverable obstruction is apparent, such as asthma, whooping cough, meningitis and congenital heart lesions. The complication of recurrent laryngeal paralysis must be considered when symptoms persist after apparently adequate reduction in the size of the gland.

4. Roentgenologic studies of the respiratory organs of infants and young children should always include the chest, neck and nasopharynx. Sagittal and lateral views must always be made during both phases of respiration, and preferably in the erect posture. The technique is fully discussed.

5. The treatment of thymic enlargement of infancy is discussed in full detail.

BIBLIOGRAPHY.

1. Lange, S.: *X*-ray Therapy of Enlarged Thymus, Am. Quart. Roentgenol., 1911, **3**, 1.

2. Marine, D.: Status Lymphaticus, Arch. Pathol., 1928, **5**, 661.

3. Kopp, J.: Denkwürdigkeiten in der ärztlichen Praxis, Frankfurt a. m., 1830, vol. **5** (referred to by Marine).

4. Jackson, C.: Thymic Tracheostenosis, Tracheoscopy, Thymectomy, Cure, J. Am. Med. Assn., 1907, **48**, 1753.

5. Jackson, C.: Peroral Endoscopy and Laryngeal Surgery, St. Louis, Laryngoscope Company, 1915.

6. Jackson, C.: Personal communication.

7. Jackson, C.: Bronchoscopy and Esophagoscopy, Philadelphia, W. B. Saunders Company, 1927.

8. Noback, G. J.: Contribution to Topographic Anatomy of the Thymus Gland, With Particular Reference to Its Changes at Birth and in the Period of the Newborn, Am. J. Dis. Child., 1921, **22**, 120.

9. Paltauf, A.: Ueber die Beziehungen der Thymus zum plötzlichen Tod, Wien. klin. Wchnschr., 1889, **2**, 877; 1890, **3**, 172. (Referred to by Marine.)

10. Wiesel, J.: Zur Pathologie des chromaffinen Systemes, Virchow's Arch. f. path. Anat., 1904, **176**, 103. (Referred to by Marine.)

11. Kundrat, R. V.: Wien. klin. Wchnschr., 1895, **8**, 1, 26, 44, 64. (Referred to by Marine.)

12. Blake, J. A.: The Surgical Aspects of Status Lymphaticus, Ann. Surg., 1902, **35**, 745. (Referred to by Marine.)

13. Symmers, D.: Status Lymphaticus, Am. J. Dis. Child., 1917, **14**, 463. (Referred to by Marine.)

14. Svehla, K.: Ueber die Einwirkung des Thymussaftes auf den Blutkreislauf und über die sogenannte Mors thymica der Kinder, Wien. med. Bl., 1896, pp. 723, 740, 757, 775, 791, 806, 821. (Referred to by Marine.)
15. Escherich, K.: Bemerkungen über den Status Lymphaticus der Kinder, Berl. klin. Wchnschr., 1896, **33**, 645. (Referred to by Marine.)
16. Pancoast, H. K., and Pendergrass, E. P.: Roentgenologic Diagnosis of Disease of the Upper Respiratory Tract in Children, Am. J. Roentgenol. and Rad. Therap., 1930, **23**, 241.
17. Pancoast, H. K.: Roentgenology of the Upper Respiratory Tract, With Special Reference to Enlarged Thymus and Its Differential Diagnosis; presented before the Interstate Post-Graduate Medical Association of North America, 1929. To be published in Transactions.
18. Pendergrass, E. P.: New Arrangement of Bucky Diaphragm for Encephalography, Am. J. Roent. and Rad. Therap., 1928, **19**, 482.
19. Remer, J., and Belden, W. W.: Roentgen Diagnosis and Therapy of the Thymus in Children, Am. J. Roent. and Rad. Therap., 1927, **18**, 119.
20. Hay, P. D.: The Neck Roentgenologically Considered, New York, Paul B. Hoeber, Inc., 1929.
21. Boyd, E.: Growth of the Thymus, Am. J. Dis. Child., 1927, **33**, 867.
22. Aldrich, C. A.: Symptoms of Vagotonia and Thymic Hypertrophy, J. Am. Med. Assn., 1930, **90**, 1119.
23. Waldbott, G. L.: Roentgen Ray Treatment of the Spleen in Asthma and in Related Allergic Disease, Arch. Int. Med., 1928, **41**, 683. (Quoted by Aldrich.)
24 Peterson, W. F.: Splanchnoperipheral Balance During Chill and Fever, Arch. Int. Med., 1927, **40**, 575. (Quoted by Aldrich.)
25. Henderson, Y.: The Prevention and Treatment of Asphyxia in the Newborn, J. Am. Med. Assn., 1928, **90**, 583.
26. Pancoast, H. K.: The *X*-ray Treatment of Leukemia and Other Diseases of the Blood-making Organs, Trans. Am. Roentgen Ray Soc., 1906, p. 169.
27. Pancoast, H. K.: Experimental and Practical Applications of the *X*-rays in Diseases of the Blood and Blood-forming Organs, Univ. of Penn. Med. Bull., 1907, **19**, 282.
28. Musser, J. H., and Edsall, D. L.: A Study of Metabolism in Leukemia, Under the Influence of the *X*-ray, etc., Univ. of Penna. Med. Bull., 1905, **18**, 174.

REMARKS ON THE PATHOGENESIS OF GRAVES' DISEASE.*

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Since Dr. Crile is to discuss the surgical treatment of goiter, while I am listed to say a few words on the etiology of Graves' disease from the standpoint of the laboratory worker, I would like to state my general view regarding the treatment of Graves' disease before going on with the main subject for discussion. I am entirely in agreement with the surgeons that in selected cases the best available treatment, at present, is a well-appointed partial thyroidectomy. I do not believe this is a rational therapy and am convinced that when the etiology of Graves' disease is fully understood, a more rational treatment will be worked out. Twenty years ago it was difficult to get an audience if one stated that the cause of Graves' disease was unknown. Today this is changed. I have long

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been one of those who believe that we must look beyond the thyroid for a solution of so complex a problem. The fact that controversy still involves every phase of the question of Graves' disease proves how complex the problem is.

Classification. The clinical manifestations are so typical and yet so atypical and variable that they have given rise to a great many classifications, even to the point of differentiating separate diseases from what is probably only varieties. This has caused a great deal of confusion. It would be much simpler and more accurate in the present state of our knowledge to divide Graves' disease primarily into *acute* and *chronic* forms, and to divide each of these headings into *complete* and *incomplete* forms. This would eliminate such terms as toxic adenoma, adenomatous goiter with hyperthyroidism, thyrotoxicosis, and a host of other more or less indefinite terms.

Pathologic Anatomy.[1] As regards the pathologic anatomy of Graves' disease, the changes in the thyroid gland have certainly been overemphasized during the past forty years. Opinions as to the significance of thyroid changes have varied from the view that they are constant and specific to the view that they are neither constant nor specific. I hold an intermediate position, namely, that they are constant but not specific. If one allows for the stage of the disease and the age of the patient it cannot be denied that hyperplasia of some degree will eventually occur in all cases if not inhibited by iodin or by some other means. I had the very fortunate opportunity between 1905 and 1915 of studying the thyroids from several hundred cases of Graves' disease in Dr. Crile's Clinic in Cleveland during our studies on endemic goiter. The hyperplasia, however, appears in no way different from the hyperplasia seen in other clinical associations. Thus iodin involutes the hyperplasia of Graves' disease as certainly as it does any other thyroid hyperplasia. The regeneration of the thyroid in Graves' disease is identical with the regeneration of the thyroid following partial removal, and we early came to the conclusion that the thyroid gland is a very labile tissue with a single definite morphologic cycle which can be repeated as often as is necessary in response to stimuli that reduce the iodin store below the critical level. When the iodin store again rises, involution to the colloid state sets in. Much has been made of the occurrence of islands of hyperplastic thyroid tissue in cases of Graves' disease with long-standing goiter. This is due to the fact that, the thyroid being a cystic organ, different groups of follicles stand in different relations to the blood supply, and those with the better blood supply regenerate earlier.

Adenomas of the thyroid as a rule do not react to iodin in this uniform manner but they tend to repeat a similar cycle in a very modified form.

The next most prominent feature of the pathologic anatomy of Graves' disease is the hyperplasia of the lymphoblastic tissues—the thymus, spleen and regional lymph glands. Markham (1856)

first noted the occurrence of thymus hyperplasia in this disease and Marie[2] (1889) was the first to suggest that the hyperplastic thymus was a regenerated thymus. Thymus hyperplasia is present in 75 per cent of complete cases occurring in individuals under thirty years of age and it is seen less frequently in cases over this age.[3] This hyperplasia of the lymphoblastic tissues is reflected in the peripheral blood as a relative lymphocytosis up to 60 per cent of all leukocytes. Theodore Kocher[4] stressed the diagnostic value of this fact, but today we do not consider it important because other clinical conditions associated with lymphoblastic overgrowth, as for example Addison's disease and status lymphaticus, also have relative lymphotoses. Lymphoid hyperplasia also occurs in the thyroid gland and is tremendously increased in cases that have been subjected to prolonged iodin medication. The significance of the thymus and lymphoid hyperplasia has been variously interpreted. Haberer[5] and von Mikulicz thought the thymus produced a toxic substance responsible for many of the symptoms and advocated thymectomy as a treatment. In this country the late Professor Halsted also did considerable work on this hypothesis. From the experimental standpoint the lymphoblastic hyperplasia looks more like an antagonistic reaction against an excessive thyroid secretion and a compensatory reaction against some suprarenal-gonadal insufficiency. Thus removal of the thyroid hastens atrophy of the thymus gland, while removal of the suprarenals in animals causes regeneration of the thymus and a clinical and pathologic condition resembling status lymphaticus. This leads to the question of the constitutional state underlying Graves' disease, the so-called Graves' constitution. Some hold that it is always congenital, but I think it also can be acquired. As we have many times pointed out, we believe that Addison's disease, Graves' disease and status lymphaticus are closely related states and that all three are intimately associated with the insufficiency of some secretion of the suprarenal cortex and gonads. In Graves' disease the suprarenals are usually small.

Last, under pathology, I would like to point out the frequency of atrophic changes in the liver. These are of the cirrhotic type and may go on to a well-marked Laennec cirrhosis. It occurs in long-standing cases and I have looked upon it as a manifestation of exhaustion atrophy.

Etiology. In the remaining time I would like to call attention to some clinical and experimental evidence which I think support the view that a deficiency of some internal secretion of the suprarenal cortex and sex glands is one of the fundamental factors in the etiology of Graves' disease, and that the thyroid changes actually represent a compensatory mechanism, although often an injurious one.

1. Sex and Age. Everyone knows that Graves' disease is from three to six times more common in the female, that is, about the same incidence as in sporadic simple goiter. The reason for this

is not yet clear. As regards age, the disease is comparatively rare before puberty and in the cases occurring after this period I think we can discern two groups: First, those from puberty to the age of thirty years and, second, those occurring during the period of decline in sexual life—in the female roughly between forty-five and fifty-five years and in the male between fifty-five and sixty-five years. The cases occurring early in life I would concede as belonging to the group with the inherited or congenital constitutional anlage which I stated a moment ago is akin to the constitutional defect of status lymphaticus, while the cases developing around the decline of sexual life belong to the group in which the constitutional defect may be acquired. Warthin recently expressed the view that you are born a potential Graves' disease or you cannot get the disease. I do not agree with this view and believe that our studies on the effects of sublethal injury of the suprarenal gland bear this out.

2. Experimental Suprarenal Cortex Injury.[7] In the rabbit and cat with intact thyroid a transient symptom complex can be produced by sufficient but sublethal injury to the suprarenals which closely resembles Graves' disease. The outstanding symptoms are increased metabolism, beginning between the third and sixth day and lasting from a week to several months, myasthenia, regeneration of the thymus and hypertrophy of the lymph glands, increased appetite, increased irritability and hypersusceptibility to drugs. This is only a crude reproduction or glimpse of the natural disease. One obvious reason for this crudeness is that the suprarenal gland is at least a dual gland whose functions are to some extent antagonistic, and in injuring the cortex we of necessity cripple the epinephrin-producing medulla. Epinephrin is the most powerful activator of metabolism known, and there is a good deal of evidence that this function is not impaired until late and may even be increased in early Graves' disease.

3. Involution of the Suprarenal Cortex in Infants.[8] A condition somewhat resembling the experimental suprarenal injuries which I have just referred to occurs normally in newborn infants, namely, the involution of the suprarenal cortex. As you know, the cortex of the newborn infant is unusually large and involution of this hypertrophic cortex begins about the eighth day of extrauterine life, irrespective of whether the infant is a full-term or a premature birth. This involution causes a striking decrease in the volume of the cortex during the next four weeks. We have shown by daily metabolism studies on 10 infants from birth to their thirty-fifth day that coëxistent with this rapid involution of the suprarenal cortex there is a rapid increase in heat production. Thus the heat production in normal infants has been found by various workers (Benedict, Murlin) to average 1.88 calories per kilogram per hour during the first seven days of life. Then between the eighth and fourteenth days it rises about 16 per cent. Our explanation of the hypertrophy of the suprarenal cortex in intrauterine life is that it

has something to do with controlling or inhibiting the rate of tissue oxidation, and after birth this overgrowth involutes in order to increase heat production.

4. Suprarenal Emulsions in the Treatment of Graves' Disease. A great number of glandular products have been used in the treatment of Graves' disease without much benefit. We have tried in an experimental way most of them, and so far have found only one that has any notable effect, namely, the suprarenal cortex.[9] Ovarian and corpus luteum emulsions have a similar but less marked effect. In over 50 cases we have found that feeding a glycerol emulsion of very fresh ox suprarenal cortex (glands from which 90 per cent of medulla has been removed) causes a striking gain in body weight and in muscle strength. These effects quite constantly begin to appear after two weeks of feeding. We have not been able to obtain these effects with air-dried preparations, and the value of the emulsion deteriorates rapidly on exposure to air. We look upon this effect as further evidence that the suprarenal cortex and sex glands produce an easily oxidizable substance which plays an important rôle in protecting the individual from Graves' disease, and the loss of which is an important factor in the cause of Graves' disease. Just as in the case of the experimental injuries to the cortex and the spontaneous involution of infants, we think the cortex produces a substance which tends to regulate or control thyroid activity, which is deficient in Graves' disease, whereas the medulla produces a very powerful activator of the thyroid secretion which is not impaired in the developmental stages of the disease.

5. Last, I would like to refer to a case of Graves' disease which more nearly suggests the experimental production of this disease in man than any of the case reports with which I am familiar. The case was called to my attention by Dr. B. S. Oppenheimer. The patient, a physician, aged about forty years, developed what was considered a retroperitoneal sarcoma and was given prolonged deep Roentgen ray therapy. After about two years of this therapy the patient first noted symptoms which later proved to be the early symptoms of Graves' disease, and after six months more of the Roentgen ray therapy he developed complete Graves' disease for which a partial thyroidectomy was performed and was followed by great improvement, though he still has marked exophthalmos and other vestigial signs of the disease. Without any knowledge of the experimental work bearing on the possible relation of the suprarenal cortex and sex glands to the etiology of Graves' disease, this patient had come to the conclusion that there was some connection between the deep Roentgen ray injury of the suprarenals and the onset of Graves' disease.

In conclusion, I would like to point out that while the view that Graves' disease is essentially a thyroid disease still is the prevailing one, and while therapy should still be based on this assumption,

I am convinced that a much more fundamental disturbance lies in a deficiency of some function of the suprarenal cortex and sex glands, which either provides another means of promoting tissue oxidations or has to do with the regulatory control of these oxidations. The most outstanding manifestation of Graves' disease is clearly a loss of control over these oxidation processes, and as a result of this there occurs a physiologic attempt toward compensation by an increased production of the thyroid hormone.

BIBLIOGRAPHY.

1. Marine, D. and Lenhart, C. H.: The Pathologic Anatomy of Exophthalmic Goiter, Arch. Int. Med., 1911, **8**, 265.
2. Marie, P.: Sur la reviviscence du thymus dans certaines affections presentant des alterations du corp thyroide etc., Bull. et mém. Soc. méd. d. hôp., Paris, 1893, 3S, **10**, 136.
3. Matti: Ueber die Kombination von Morbus Basedowii mit Thymushyperplasie, Deutsch. Ztschr. f. Chir., 1912, **116**, 427.
4. Kocher, T.: Untersuchungen des Blut im Basedowii Krankheit, Arch. f. klin. Chir., 1908, **87**, 87.
5. Von Haberer, H.: Ueber die klinische Bedeutung der Thymusdrüse, mit spezieller Berücksichtigung des Morbus Basedowii und des Status thymicus, Med. Klin., Berlin, 1914, **10**, 1087.
6. Halsted, W. S.: Significance of the Thymus in Exophthalmic Goiter, Johns Hopkins Hosp. Bull., 1914, **25**, 223.
7. Marine, David and Baumann, Emil J.: Effect of Suprarenal Insufficiency (by Removal or by Freezing) on the Respiratory Exchange in Rabbits, Am. J. Physiol., 1921, **57**, 135.
8. Marine, D., Lowe, Blanche H. and Cipra, Anna: The Possible Influence of Suprarenal Involution in Newborn Infants on Heat Production, Jour. Metab. Res., 1922, **2**, 329.
9. Shapiro, S. and Marine, David: Clinical Report of a Case of Graves' Disease with Rapid Improvement Following the Oral Administration of Fresh Ox Suprarenal Cortex, Endocrinology, 1921, **5**, 699.

THE SIZE OF THE HEART IN GOITER.

A Teleroentgenographic Study.

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The question of cardiac enlargement as the result of hyperthyroidism has long been unsettled. One gains an impression from the literature that cardiac enlargement from hypertrophy or dilatation,

or both, is a frequent finding in hyperthyroidism and that it is due in some way to the disease in question. Many statements have been made without adequate statistical evidence to support them. We felt it desirable, therefore, to study by Roentgen ray a consecutive series of 100 patients with hyperthyroidism and compare it with an equal number of patients with nontoxic goiter.

In determining the size of the heart in any individual, the question of slight degree of hypertrophy or dilatation is difficult to settle. Most of the methods in present-day use for determining the size of the heart correlate the area of the frontal silhouette as determined by orthodiagraphic tracing, and the body weight or height, or both. It is obvious that in a group of patients who have lost weight, particularly when the weight loss has been excessive or the patient has been unable to estimate the weight loss, this method of determining heart size is open to question, particularly when slight enlargement is to be decided upon. We have, therefore, simply recorded the heart measurements from teleoroentgenograms in a series of consecutive cases. A few were discarded because of various deformities of the chest or spine. Fortunately, we found that the age distribution was similar in both groups so that justifiable comparisons could be made (Table I).

TABLE I.—AGE DISTRIBUTION BY DECADES IN THE TOXIC AND NONTOXIC GROUPS.

Decade.	Toxic group.	Nontoxic group.
15 to 19	3	1
20 to 29	11	11
30 to 39	22	28
40 to 49	31	30
50 to 59	26	24
60 to 69	7	6
Totals	100	100

The radiographs of the heart in this series were taken at the usual 7-foot distance, with the patient holding his breath neither in full inspiration nor full expiration. This necessarily resulted in some movement and in different degrees of chest expansion, but we felt that the heart shadow would perhaps be quite as near normal and would vary no more than if taken in other ways.

Heart disease may occur in patients with goiter as well as in any other group of individuals. This must be taken into consideration before ascribing cardiac enlargement to goiter. In fact, it has been our clinical impression, based on the examination of many thyroid patients, that in most instances cardiac enlargement in patients with hyperthyroidism is usually associated with some independent cardiovascular disease. In the study of any group of individuals one finds a certain number with cardiac enlargement without obvious clinical or anatomic cause. This group displaying cardiac enlargement would, in most instances, fall in the fourth to sixth decade.

Without known etiology the enlargement would probably be classed clinically as myocarditis or arteriosclerotic heart disease. Plummer[1] reported in 1922 the finding of 63 cases of cardiac enlargement in a series of 617 cases of nontoxic goiter, none of which patients showed hypertension clinically, or other etiologic factors, aside from the presence of goiter. Cabot,[2] in an analysis of 662 postmortem cases of hypertrophy and dilatation of the heart, found 154 cases without any anatomic cause. Bolinger,[3] in Germany, found, on the basis of 1000 postmortem cases, 43 cases of cardiac hypertrophy, also without obvious anatomic cause. (These he ascribed to the excessive amount of beer which was drunk in Munich.) These references are cited merely to show that there are still unexplained causes of cardiac hypertrophy and dilatation. One must, therefore, be careful in ascribing an enlarged heart to goiter when no other anatomic cause can be found.

Diagnosis of Coincident Heart Disease. The diagnosis of coincident heart disease in the presence of hyperthyroidism is frequently difficult. For this study we have classified coincident cardiovascular disease under three headings: that is, rheumatic, hypertensive and miscellaneous. (*a*) Under "rheumatic" were included those cases which showed unquestionable evidence of valvular disease such as mitral stenosis and aortic regurgitation, with or without a history of rheumatic fever or chorea. Others with less marked evidence, that is, mitral regurgitation, who had a history of rheumatic fever, were classified as rheumatic heart disease. Most of these have been seen since operation and the character of the murmur has not changed. (*b*) Hypertension was diagnosed, with the exception of 5 cases, in patients over forty years of age who showed a basal systolic blood pressure of not less than 150 mm. Hg. Other evidence was used, such as changes in the retinal or peripheral vessels. A number of these patients showed a basal diastolic pressure over 100 mm. Hg. before operation, and most of them showed it after operation. We know that this criterion does not include all hypertensive cases, but, on the other hand, of 26 toxic cases so diagnosed 25 showed distinct and well-marked hypertension three months or more after operation. Furthermore, we know from follow-up study of the blood pressure after operation for toxic goiter that the incidence of hypertension in this series is that which is to be expected according to each age group.[4] (*c*) Under the miscellaneous group were placed those patients who showed evidence of coronary disease and angina pectoris; there was one case of pericardial effusion, one case of acute glomerular nephritis with generalized edema and enlarged cardiac shadow. A diagnosis of arteriosclerotic heart disease was not made in this study because we felt that cardiac enlargement might thus be too easily accounted for and, therefore, subject to criticism. While we know that it existed, we have avoided using it. There were no cases of luetic aortitis found in this series.

The statistical data of the two groups is shown in Tables II and III. It should be mentioned here that the incidence of toxic adenomatous goiter in this series of 100 was higher than we usually find. Furthermore, we found rheumatic fever and rheumatic heart disease present in this group more frequently than we usually encounter it. This was probably largely a matter of chance but, insofar as this study is concerned, it should favor the finding of larger heart measurements in toxic goiter.

TABLE II.—MISCELLANEOUS DATA.

Item.	Toxic goiter.	Nontoxic goiter.
Average first basal metabolic rate	+48.04	+4.5
Average first basal pulse	103	80.9
Average first basal weight in pounds	124	139
Average weight loss in pounds	23.2	0
Average first basal blood pressure	145/70	136/73
Average first clinical blood pressure	163/79	144/86

TYPE II A.—MISCELLANEOUS DATA.

	Toxic goiter.	Nontoxic goiter.
I. Sex:		
a. Males	16	6
b. Females	84	94
II. Type goiter:		
a. Exophthalmic goiter	61	0
b. Recurrent exophthalmic goiter	6	0
c. Adenoma	11	44
d. Multiple adenoma	22	52
e. Malignant adenoma	0	4
III. Arteriosclerosis:		
a. Calcified aortic plaques	8	7
IV. "Rheumatic infection:"*		
a. Growing pains	6	10
b. Tonsillitis	37	34
c. Quinsy sore throat	6	2
d. Chorea	1	0
e. "Rheumatic fever"	19	6

* Rechecked by letters to patients.

INCIDENCE OF CARDIAC ENLARGEMENT. We have arbitrarily chosen cardiac enlargement to mean a transverse diameter of the heart which was 0.9 cm. or more over one-half the inside diameter of the chest. It is obvious that this did not include some cases of cardiac enlargement, but on the other hand cases are also present in this group which are not actually enlarged, particularly in the transverse type of heart. Of the total number, 46 per cent of toxic cases showed cardiac enlargement according to the above standards, while 41 per cent in the nontoxic group were enlarged. Certainly, this is not a striking difference.

RELATIONSHIP TO AGE. In Table III the percentage of heart enlargement is shown according to age group. It is to be noted that where the percentage in the different groups is based upon enough cases to be significant, the number of enlarged hearts appears

to increase with age. These figures parallel closely those published by Coller on "The Heart in Endemic Goiter."[5]

TABLE III.—CARDIAC ENLARGEMENT (0.9 CM. OR MORE OVER CARDIOTHORACIC RATIO OF 1 TO 2) ACCORDING TO AGE GROUPS.

Age groups.	Toxic goiter. Total cases.	Toxic goiter. No. of cases C.T. ratio over 0.9 cm.	Toxic goiter. Per cent C.T. ratio over 0.9 cm.	Nontoxic goiter. Total cases.	Nontoxic goiter. No. of cases C.T. ratio over 0.9 cm.	Nontoxic goiter. Per cent C.T. ratio over 0.9 cm.
10 to 19	3	1	33	1	0	0
20 to 29	11	3	27	11	2	18
30 to 39	22	9	45	28	9	32
40 to 49	31	15	45	30	13	43
50 to 59	26	14	53	24	13	54
60 to 69	7	4	57	6	4	66
Totals	100	46	46	100	41	41

RELATIONSHIP OF CARDIAC ENLARGEMENT TO THE DURATION OF HYPERTHYROIDISM. Table IV shows the measurements of the heart as compared with the duration of thyroid toxicity. There seems to be no definite relationship. We feel, however, that this is not absolutely conclusive, since the number of cases of long duration is not sufficient to give reliable averages.

TABLE IV.—CARDIAC ENLARGEMENT (0.9 CM. OR MORE OVER CARDIOTHORACIC RATIO OF 1.2) GROUPED ACCORDING TO ESTIMATED DURATION OF DISEASE—TOXIC GOITER (DURATION UNDETERMINED IN 11).

Duration, months.	No. of cases.	No. of cases C.T. ratio over 0.9 cm.	Per cent C.T. ratio over 0.9 cm.
1 to 11	45	19	42
12 to 23	22	12	54
24 to 35	12	5	41
36 to 47	3	0	0
48 to 59	7	3	42
	89	39	43.8

TABLE V.—CARDIAC ENLARGEMENT (0.9 CM. OR MORE OVER CARDIOTHORACIC RATIO OF 1 TO 2) GROUPED ACCORDING TO ESTIMATED WEIGHT LOSS (89 CASES).

Pounds lost.	*Toxic Goiter.* Total cases.	No. of cases C.T. ratio over 0.9 cm.	Per cent C.T. ratio over 0.9 cm.
0 to 9	13	3	23
10 to 19	32	17	53
20 to 29	21	11	52
30 to 39	9	4	44
40 to 49	11	5	45
50 to 59	2	1	50
60 to 69	1	1	100
Totals	89	42	48

RELATIONSHIP OF CARDIAC ENLARGEMENT TO WEIGHT LOSS. An attempt at correlation between the size of the heart and weight loss is shown in Table V. Again no definite relationship is forthcoming.

We realized here, too, that to come to a definite conclusion in regard to weight loss, which in many instances is a sign of the severity of the disease, we should exclude all cases of known heart disease and compare a large number of such cases who show extreme amounts of weight loss with a group that has lost very little.

A Comparison of the Degree of Cardiac Enlargement in the Two Groups. The cases were divided into five groups as follows: The first group consisted of those in which the transverse diameter of the heart was less than, or equal to, one-half the transverse diameter of the chest; the second group included those in which the transverse diameter of the heart exceeded one-half the transverse diameter of the chest by 0.1 to 0.9 cm.; while the other three groups included those in which the transverse diameter of the heart exceeded the transverse diameter of the chest by 1 to 1.9 cm., 2 to 2.9 cm. and 3 cm. or more, respectively (Table VI). The parallelism in the two groups of goiter is striking.

Table VI.—Various Cardiothoracic Ratios in Toxic and Nontoxic Goiter.

	Toxic goiter.	Nontoxic goiter.
Transverse diameter of heart equal or less than one-half transverse diameter of chest	27	29
Transverse diameter of heart 0.1 to 0.9 cm. (inclusive) greater than one-half transverse diameter of chest	27	30
Transverse diameter of heart 1 to 1.9 cm. (inclusive) greater than one-half transverse diameter of chest	24	15
Transverse diameter of heart 2 to 2.9 cm. (inclusive) greater than one-half transverse diameter of chest	11	16
Transverse diameter of heart 3 cm. or over greater than one-half transverse diameter of chest	11	10
Total cases	100	100

The Correlation Between Age Group, Cardiothoracic Ratio, Type of Goiter and Heart Diagnosis. This distribution for the toxic cases is shown in Table VII. It is to be noted that a greater percentage of hearts apparently enlarged fall in the toxic adenomatous group (66 per cent of toxic adenomatous group enlarged, compared with 35 per cent for exophthalmic goiter), but it also can be seen that those with toxic adenomatous goiter fall mainly in the fourth, fifth and sixth decades. This can account for the greater frequency of cardiac enlargement, due to the greater incidence of cardiovascular disease. Table VIII shows the same correlation for nontoxic cases, except that the discrete adenomas of the thyroid were separated from the multiple adenomatous type. Fifty per cent of the patients with multiple adenomatous goiter showed an increase over the so-called normal cardiothoracic ratio of 1 to 2 by 0.9 cm., whereas only 36 per cent of the cases with single adenoma showed this change. A greater incidence of hypertension in the multiple adenomatous group probably explains this

difference. It might be well to say here that a good many patients are sent to us with hypertension and goiter with the prevalent idea that the two are associated. Thus, a patient who has had a goiter for years might not be taken seriously by his physician, but as soon as a high blood pressure is found operation is then considered.

TYPE VII.—TOXIC GOITER. DISTRIBUTION BY AGE, TYPE OF GOITER, HEART DIAGNOSIS AND HEART MEASUREMENTS. TRANSVERSE DIAMETER OF HEART IN CENTIMETERS OVER CARDIOTHORACIC RATIO OF 1 TO 2.

Age group.	Exophthalmic goiter.				Toxic adenomatous goiter.			
	To 0.9 cm.	1 to 1.9 cm.	2 to 2.9 cm.	3 cm. +.	To 0.9 cm.	1 to 1.9 cm.	2 to 2.9 cm.	3 cm +.
10 to 19	2 N	1 R						
20 to 29	7 N	2 N						
	1 R	1 H						
30 to 39	9 N	2 N	1 M	..	1 N	1 R		
	1 H	2 R	2 R	..	2 H			
		1 H + R						
40 to 49	9 N	1 N	2 H	1 R	1 R	1 N	1 R	1 H + R
	1 M	3 H	..	..	...	3 H	...	1 H
	3 R	1 H + R						
	2 H							
50 to 59	3 N	1 N	1 R	..	3 N	...	2 H + R	2 H + R
	1 M	2 H	..	..	3 H	...	1 M	2 H
	1 R	1 M	..	..	1 H + R	...	1 H	1 R
60 to 69	1 N	...	..	..	1 N	1 H + R	...	1 H
	1 H	...	..	..	...	...	...	1 R
								1 H + R

N = Negative findings. H = Hypertension. R = Rheumatic or probable rheumatic valvular disease. M = Miscellaneous.

TABLE VIII.—NONTOXIC GOITER. DISTRIBUTION BY AGE, TYPE OF GOITER, HEART DIAGNOSIS AND MEASUREMENTS. TRANSVERSE DIAMETER OF HEART IN CENTIMETERS OVER CARDIOTHORACIC RATIO OF 1 TO 2.

Age group.	Single adenoma.				Multiple adenoma.			
	To 0.9 cm.	1 to 1.9 cm.	2 to 2.9 cm.	3 cm. +.	To 0.9 cm.	1 to 1.9 cm.	2 to 2.9 cm.	3 cm. +.
10 to 19 . .	....	..	..	..	1 N			
20 to 29 . .	3 N	..	..	..	4 N	2 N		
	1 H	..	..	..	1 H			
30 to 39 . .	11 N	1 N	2 N	1 H	7 N	1 R	1 R	
	1 R	1 R	1 R	1 M				
40 to 49 . .	9 N	1 R	1 H	..	6 N	2 N	2 N	1 N
					2 R	2 H	3 H	1 H
50 to 59 . .	5 N	2 H	1 N	..	2 N	1 N	1 H	2 H + M
	2 H	..	1 H	..	1 H	2 H	...	1 N
	1 H + R	..	..	..	..	..	...	2 H
60 to 69 . .	1 N	..	1 R	..	1 H	..	1 H	
							1 H + R	

N = Negative clinical findings. H = Hypertension. R = Rheumatic or probable rheumatic valvular disease. M = Miscellaneous.

CORRELATION BETWEEN WEIGHT AND HEART SIZE. We have further distributed these cases according to cardiothoracic ratio, correlating the average weight for each group, the transverse diameter of the chest and the transverse diameter of the heart. This is shown in Table IX. This was done to exclude a possible error in using the cardiothoracic ratio as an index to heart size rather than the area of the frontal plane correlated with body weight. The average weight for the different groups, both toxic and nontoxic types, varies but little. If the average weight loss was 23.2 pounds and was added to each group of toxic goiter, the average weight of both groups would be practically the same, at least so far as it might influence the size of the heart. The transverse diameter of the chest, however, is greater in those groups where the cardiothoracic ratio is normal or below. This might indicate that a number of these hearts were enlarged, but the parallelism of the average transverse diameters of the heart in the two groups would seem to offset this impression.

TABLE IX.—DISTRIBUTION ACCORDING TO VARIOUS CARDIOTHORACIC RATIOS WITH AVERAGE TRANSVERSE DIAMETER OF HEART AND CHEST AND AVERAGE WEIGHT.

Variation from the "normal" C.T. ratio (1 to 2) in centimeters.	Nontoxic goiters.			Toxic goiters.		
	T.D. chest (cm.).	T.D. heart (cm.).	Average weight in pounds.	T.D. chest (cm.).	T.D. heart (cm.).	Average weight in pounds.
− to 0	25.6	11.8	148.0	24.3	11.3	120.0
+0.1 to 0.9	23.6	11.8	141.0	23.8	12.3	120.0
+1.0 to 1.9	24.2	13.1	146.7	23.9	13.4	122.3
+2.0 to 2.9	23.2	13.9	152.0	22.2	13.9	125.2
+3.0	23.9	16.2	151.0	22.5	14.9	120.8

TABLE X.—COMPOSITE HEART AND CHEST MEASUREMENTS.

	Toxic goiter (100 cases), cm.	Nontoxic goiter (100 cases), cm.
Transverse diameter chest (average)	24.1	23.95
Transverse diameter heart	13.01	12.52
Left border	9.04	8.63
Right border	3.96	3.89
Long diameter	13.67	13.28

Discussion. If hyperthyroidism produces any great enlargement of the heart one might reasonably expect to find greater average measurements in a group, such as we have studied. In Table X is given the composite picture of the heart measurements in both groups. These measurements represent simple averages. With the average transverse diameter of the chest the same in both groups, and with the average weight of the nontoxic group within 2 pounds of the estimated average weight in the toxic group based on average weight loss, we believe it is possible to make comparisons

in regard to the actual heart measurements. Accordingly, we find that the average transverse diameter of the heart in the toxic group exceeds the average transverse diameter of the nontoxic group by only 0.49 cm. There is no question that cardiac enlargement, as a result of thyroid toxicity, must be made on a large group and not on individual cases. One must, therefore, conclude that if hyperthyroidism causes cardiac enlargement, that is, hypertrophy or dilatation or both, it does so only to a slight degree. One can hardly conceive of the heart not increasing in weight at least slightly as the result of the excess activity, yet it is remarkable that even in long-standing hyperthyroidism of high degree in younger people the heart is often found to be of normal size. Recent experimental work[4] has shown some hypertrophy of the heart involved after relatively large doses of thyroid extract in dogs. One cannot reproduce a similar experiment in the human being, but, could it take place, a greater degree of cardiac enlargement than found in this series would be expected.

It might reasonably be asked, is the cardiac enlargement in the nontoxic group herein reported due to the so-called goiter heart from tracheal stenosis? Meyer and Sulger[7] state that the largest hearts are found in cases with tracheal stenosis. In 125 cases of toxic and nontoxic goiter they found the heart enlarged in 66 cases. Fourteen of these cases, however, showed no thyroid toxicity and no tracheal pressure. Of these 14, 1 was rheumatic, 1 arteriosclerotic and a third had "myocarditis." No reference was made in their study of the age of the patients or blood-pressure determinations. In our toxic cases the largest hearts were associated with tracheal narrowing in only 3 cases and none of these were compressed enough to cause stridor on exertion or at rest. Nor was stridor present in any of the series of nontoxic goiter, but various degrees of tracheal pressure were present. Of those patients in the nontoxic group showing cardiac enlargement without obvious clinical cause, only one showed tracheal narrowing. In a community such as New England where endemic goiter is not prevalent, few cases of severe tracheal stenosis are seen. Thus, our findings may not parallel those found in a goiter belt. The same might be said also of the incidence of rheumatic fever, or rheumatic heart disease associated with goiter in different localities.

In order to exclude the possibility of a low-grade toxemia of some kind affecting the heart, which has often been suggested[6] in nontoxic goiter, we have undertaken a study of 100 Roentgen rays of nongoitrous individuals of the same age distribution as found in this series.

Conclusions. 1. Teleroentgenograms were made on 100 consecutive cases of toxic and 100 consecutive cases of nontoxic goiter in the Lahey Clinic.

2. No definite relationship could be found between the duration of the disease or weight loss and the size of the heart.

3. Cardiac enlargement as determined by teleoroentgenography showed a fairly direct relationship to age and coincident cardiovascular disease.

4. The number of enlarged hearts of different degrees was practically the same in both toxic and nontoxic goiter.

5. If hyperthyroidism causes cardiac enlargement or hypertrophy and dilatation, it is slight.

REFERENCES.

1. Plummer, H. S.: Blood Pressure and Thyrotoxicosis, Trans. Assn. Am. Phys., 1915, **30**, 450.
2. Cabot, R. C.: Facts on the Heart, W. B. Saunders Company, Philadelphia, 1926, p. 424.
3. Bolinger, Prof.: Über die Häufigkeit von Ursachen der idiopathischen Herzhypertrophie in München, Deutsch. med. Wchnschr., 1884, **10**, 180.
4. Hurxthal, L. M.: The Blood Pressure Before and After Operation in Hyperthyroidism (in press).
5. Coller, F. A.: The Morbidity of Endemic Goiter, J. Am. Med. Assn., 1924, **82**, 745.
6. Simmons, J. P., and Brandeis, W. W.: The Size of the Heart in Experimental Hyperthyroidism, Arch. Int. Med., 1930, **45**, 503.
7. Meyer, A. W., and Sulger, E.: Das Kropfherz vor und nach Operation, Med. Klin., 1926, **1**, 838.

EDEMA.

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The factors responsible for the presence of edema have always been sought for in some change in the local physicochemical factors on one or the other side of the capillary wall or in a change of permeability in the capillary wall itself. There are many reasons why such changes in the local physicochemical factors or in the permeability of the capillary walls are not sufficient to explain the formation of edema. Lately the tendency has been to look for the causes of edema in a disturbance of the water regulation as a whole. Local physicochemical changes alone are never adequate to explain a disturbance in a vegetative function. Although at the bottom of every physiologic process in the organism there is a physicochemical change yet the totality of the process is different from that which takes place in an artificial physicochemical system. The difference is that between physiology on one hand and chemistry and physics on the other. Physiology implies regulation of the physicochemical changes and such a regulation has been developed for each physiologic process phylogenetically for a purpose. The purpose is that of maintaining the physiologic process constant or near-constant under varying conditions. Haldane[1] years ago in a Harvey lecture spoke of the physiology of the normal, meaning thereby that we

have to determine how the organism maintains the various normals. This has been most clearly expressed by Claude Bernard.[2] He saw that in the more highly developed organism a free and independent life can only be maintained if the organism is able to maintain a constant and uniform internal milieu in contrast to the every-changing external milieu. As the individual factors of the internal milieu which must be kept at a constant value, Claude Bernard mentions water, oxygen, heat and the chemical and food reserves. The maintenance of constant values is of such importance to the physiologic organism that we can express as a fundamental principle in physiology:

I. The organism attempts to maintain constant values within the normal limits of variation for those substances which it needs in its economy and for those processes to which it has become adapted phylogenetically.

Such constant values are familiar to us in the number of red blood corpuscles in the blood, in the amount of hemoglobin, of sugar, of fat, of salts, and of protein in the blood, in the maintenance of the body temperature, of the degree of oxidation, and of many other vegetative functions. Such constant values are maintained by effector organs which are under the control of the central nervous system, as already indicated by Claude Bernard.

II. It is obvious to ordinary observation that the water content of the highly developed organism is maintained at a constant value. The weight of the individual under uniform external conditions and uniform food intake is practically constant from day to day and is quite independent of the amount of water taken in. An excess of water taken in is promptly eliminated. Water in the organism is contained in the blood stream, in the lymph stream, and in the organs and tissues. The water content of the blood is always found to be constant within the normal limits of variation. And this is as it should be, for were the blood volume to change continually, the maintenance of a constant internal milieu, or for that matter, of the whole circulation, would not be possible. As a matter of fact, the water content of the blood is hardly ever disturbed over a prolonged period, even under pathologic conditions.

The amount of lymph is extremely variable, and dependent entirely upon the activity of the organ from which it comes. When the organ is active the amount of lymph is increased. It evidently forms a buffer between the active organ and the blood stream, and takes up the excess of waste substances and of water.

In the organs and tissues, water is contained as bound water, forming part of the colloidal system of the protoplasm and as free water, which is found between the individual parts of the protoplasm and between cells and tissues. The free water is a variable quantity and varies from hour to hour with the intake of water and with its elimination.

In the colloidal system of protoplasm, the solid phase consists of particles of protein, nucleoprotein and lipoids in combination with electrolytes, and the liquid phase consists of a solution of protein and electrolytes. This system presents an enormous intersurface on which the fundamental biologic processes of oxidation and respiration take place. The stability of such a system is maintained by the difference in potential of the two phases. The electrolytes concerned are hydrogen, hydroxyl, chlorid, phosphate, sulphate, sodium, potassium, calcium, magnesium. A change in the electrolytic distribution produces a change in the phases of the colloidal system, and water is either taken up by the system or given off. The system is in equilibrium with the free water between the individual parts of the protoplasm and between the cells. Water taken up by the system comes from the free water, and water given off goes to increase the free water. Any change in the system must always be preceded by a change in the electrolytic distribution in the phases of the system.

Thus, the water contained in the body is maintained at a constant value in the blood; varies in the colloidal system of the protoplasm with the changes in the fundamental biologic processes of the protoplasm and shows greater variations in the free water in the tissues and in the lymph stream. The total water content in the body is, however, constant from day to day under uniform conditions.

Water in the organism moves continually; excretion through the kidneys is continuous, similarly through the lungs, through the skin and through the intestines. The water so lost is made up from free water of the tissues. There is thus a continuous movement of water from the tissues to the blood stream. Water is continually taken in to make up for the water lost.

What happens when water is ingested into the alimentary tract?

III. Water taken into the alimentary tract is absorbed into the blood stream in the form of an isotonic solution. The ingestion of water thus starts a series of changes in the body, beginning with the movement of salt to convert the water into an isotonic solution, and followed by the absorption of water into the blood stream. The changes that occur after absorption have been studied by numerous observers who investigated the changes in the water content of the blood and of the various organs and tissues. The most noteworthy studies in this direction are those of Marx.[3] He made numerous hemoglobin determinations with an exact hemoglobinometer before and after drinking 50 to 2000 cc. of water or weak tea. He found that after drinking there is always a reduction in the hemoglobin in the first twenty to forty minutes. This initial dilution is followed in fifty to eighty minutes by an increase in the concentration of the hemoglobin to the original figure. This is followed by a second dilution, which is less steep than the first, but lasts longer. In about four to five hours the original fasting value is reached.

Marx also found that the initial dilution is not proportional to the fluid intake. In many of his observations there was an equal dilution whether the fluid intake was a 1000, 500, 125 or 50 cc. The dilution could not therefore be explained by the amount of the ingested water. It was necessary to assume that the ingested water, whether large or small, started complicated exchange processes between the blood and the tissues. Marx even obtained the same curve of blood dilution when the drinking of water was suggested to an individual in hypnosis.

IV. While this dilution of the blood stream is going on the ingested water is absorbed from the alimentary tract into the blood stream. The excess of water is eventually eliminated through the kidneys but diuresis does not begin until about fifty to sixty minutes later and is prolonged over hours. Meanwhile the water has left the blood stream and has passed into the tissues. It is necessary that we know where this water goes to.

Studies of the water content of organs and tissues have been made by Magnus,[4] Engels,[5] Wahlgren,[6] Tashiro,[7] Baer,[8] and others. It has been definitely shown that the water leaving the blood stream is taken up by various organs, especially the muscles and the skin, and particularly the connective tissue of these organs. The free water there is thus increased and we have in the muscles and the skin depots which the organism makes use of to store any excess of water. The living muscle of a rabbit showed an increase in weight after the ingestion of water and a diminution in weight after the abstraction of water by means of the intravenous injection of hypertonic salt solutions.

In addition to the muscles and the skin, another organ is concerned in the taking up of water, namely the liver. It has been shown by Lamson and Roca[9] and by Pick and his associates,[10] that the liver easily takes up fluid temporarily and acts as a reservoir. In a dog with an Eck fistula, that is, one in which the greater part of the liver is excluded from the circulation, the ingested water begins to appear in the urine in from twenty to thirty minutes, while in the animal with the liver intact it appears in from fifty to sixty minutes.

The spleen as a reservoir for the blood has been considered by Barcroft.[11]

The liver, muscles and skin thus take up the ingested water, and after a period the excess of water in the depots gradually flows back into the blood stream to be excreted by the kidneys. Excretion continues until all the excess is removed and the mean normal is retained.

The organs mentioned, namely, the muscles, skin, liver and kidneys, form a group of effector organs among whose functions there is also that of taking up the excess of water and gradually eliminating it from the body. There is a continuous movement of water

from the alimentary canal into the blood stream, into the water depots, back again into the blood stream, to be eliminated by the kidneys and extrarenally by the lungs, the skin and the intestinal tract.

These organs form thus a unitary mechanism and their function as far as the taking up and giving off of water is concerned, must be considered as a unit. Water moves in these organs to and from the blood stream, through tissues and membranes which form barriers, and through which it moves at varying rates of speed.

In connection with the water content of these organs the sodium chlorid content must be considered. When an excess of salt is taken in, it is absorbed into the blood stream and from there wanders into certain depots, chief of which are the muscles and the skin. Water is retained with the salt, and whenever water moves in the body it does so in the form of a saline solution. When there is an excess of salt in the tissues an extra amount of water is retained. A change in the rate of movement of sodium chlorid necessitates also a change in the rate of water movement.

V. The organs mentioned above, namely, the muscles, skin, kidneys and also the liver, constitute a mechanism for the maintenance of the normal water content of the internal milieu. As they constitute the effector organs in the maintenance of a vegetative function they must be coördinated in an exact manner. The exact coördinated action of such a mechanism, the effector organs of which are so widely distributed throughout the body, can only be attained by means of the central nervous system. This was the understanding of Claude Bernard. It is a fundamental principle of physiology that every vegetative function necessitating the maintenance of a constant value has a central coördinating regulation. We may accept as fundamental that such regulation is effected, first peripherally, that is, in the effector organs themselves, by means of a physicochemical system; second, centrally, by means of the vegetative nerves presided over by a center in the brain; third, by means of hormones. Every complicated vegetative function is regulated in this manner and we can only have a full understanding of such a function when we have a full understanding of the manner in which it is regulated.

In the peripheral effector organs the particular function is performed in the colloidal system of the protoplasm. The performance of the function is dependent upon the distribution of the electrolytes in the phases of the colloidal system. A change in the distribution of the electrolytes means a change in the character or intensity of the function, either an increase in function or a decrease. Of the electrolytes concerned we know that hydrogen, hydroxyl, calcium, sodium and potassium are especially important. We also know that antagonistic influences are exerted by hydrogen and hydroxyl ions, also by calcium on the one hand and sodium and

potassium on the other. Other electrolytes such as magnesium, iron, sulphate and phosphate are also of importance, but we may take the first named as the best known in their action.

These problems have been studied especially in the school of Kraus, and those who are interested in them will find a careful consideration of the functions of the electrolytes in physiologic processes in the work of Zondek.[12]

Kraus and Zondek have come to the conclusion that the influence of the vegetative nerves on the colloidal system of the cell is through the electrolytes. The two antagonistic nerves, namely, the sympathetic and the parasympathetic, exert their influence by changing the distribution of electrolytes in the colloidal system of the protoplasm. Their influence on the function of the cell is therefore identical with that of certain electrolytes, and their antagonism to one another is dependent upon the antagonistic influence of certain electrolytes. The influence of the sympathetic nerve is identical with that of calcium, and the influence of the vagus with that of potassium. Kraus and Zondek speak, therefore, of the vegetative system, including under this term the vegetative nerves, their centers in the brain, and the electrolytes in the periphery which they influence. The vegetative system changes the function of the effector organs either by increasing the rate at which the individual function is performed or by diminishing the rate.

As the change in the rate at which a function is performed in the cell can only be produced by a change in the electrolytes, it is evident that the action of drugs or poisons must also be on the electrolytes. The action of certain drugs on the cells is therefore identical with the action of the nerves, and the antagonistic influences of certain drugs on the function of the cell is identical with the antagonistic action of the electrolytes and of the vegetative nerves. Hormones produced in the body are such drugs and their influence on certain cells is therefore identical with the influence of nerves and electrolytes on the cell. The identical action of adrenalin, of the sympathetic nerves fibers and of calcium is well known. Such hormones serve as a third means of regulating the rate of function of the effector cells and organs.

To us it is of interest to know how the function of the effector organs concerned in the water exchange is regulated in this threefold manner, by means of electrolytes at the periphery and centrally by the vegetative nerves and by certain hormones.

VI. We have considered the effector organs for the water exchange in the body, namely, the muscles, skin, kidneys and liver as a unitary mechanism which has as its function the maintenance of the normal water content of the body and especially of the blood stream. Water moves continuously through these organs, and the rate of motion is dependent upon the intake of water and upon the control exercised on the rate of motion. It is obvious that when

the rate of motion of water in one of these organs is either increased or diminished, the rate of motion in the other organs of this mechanism must also be increased or diminished. Otherwise the water content of the blood will rapidly become increased or diminished.

What influences the rate of motion of water locally? Water moves from its depots to the blood stream through barriers made up of layers of tissues. Reid[13] long ago and, more recently, Wertheimer[14] and Mond,[15] among others, have studied the passage of water through many-layered living membranes. It was found that water does not move through a living membrane of many layers in the same manner as it does through a dead membrane. In the living membrane the rate of water through it and the degree of permeability for water on one side or the other, is dependent upon the electrolytic content of the water and upon the ability of the individual layers to take up water; the latter again is dependent upon the electrolytic content of the individual layers. These investigations show that the permeability of the living membrane and the rate of water through it can be influenced by a change in the electrolytic content of the water.

Here we have experimental evidence as to the manner in which the rate of movement of water from their depots to the blood stream is affected, namely, by a change in the distribution of the electrolytes. This is the peripheral physicochemical regulation of water movement in the body. It is obvious that when a change in rate of water movement is produced in some part of the mechanism for water exchange, a corresponding change of rate must be produced in the other parts. Such a corresponding change can only be effected through a central nervous regulation. Wertheimer[14] has also shown that the water content of muscle tissue can be influenced by the vegetative nerves. In accordance with the view that vegetative functions are controlled by the vegetative system, we must assume such a regulating control by the vegetative nerves on the electrolytes of the tissue membrane barriers through which water moves. It is also clear that we must look for a center in the brain for the seat of such central regulation.

It is unnecessary to enter here into the details of all the experiments concerned. From the time of Claude Bernard investigators have busied themselves with the study of the central regulation of water exchange especially in connection with diabetes insipidus. Through the work of Eckhard,[17] Aschner,[18] Camus and Roussy,[19] Houssay,[20] Leschke,[21] Bailey and Bremer,[22] Curtis,[23] Pohle,[24] Jungmann and Bernhardt,[25] and numerous others, it has been definitely established that in the hypothalamus, in the gray matter surrounding the third ventricle, a center is situated which influences the rate of water movement through the tissues and kidneys. Increase in the rate of water movement can be produced by injury to this center. A change in water movement resulting in a slower rate

from the tissues to the blood stream than in the opposite direction has also been produced. It is clear that when the water movement from the tissues to the blood stream is slower than the movement of water in the opposite direction that the continuous intake of water must result in an accumulation of water in the tissues.

It is important to keep in mind that this center is situated in that portion of the gray matter which contains centers for numerous vegetative functions, perhaps for all. It contains centers for the regulation of salt in the body, for the rate of metabolism, for the regulation of carbohydrate, fat and protein metabolism, for respiration, circulation, blood pressure, uterine contraction and for other functions.

So much for the second mode of regulation, that is, by means of the nervous system.

VII. The third mode of regulation—that by means of hormones—also occurs. There are especially two hormones whose effect on the water exchange is well known, that of the thyroid gland, and that of the posterior lobe of the hypophysis. Eppinger[26] has studied the action of the thyroid gland on the water exchange and has shown that its effect is to increase the rate of water movement. Part of this action is due to the increase in the metabolic rate and part of it is probably due to its effect on the separating membranes through which water moves.

Of greater importance is the effect of the hormone of the posterior lobe of the hypophysis. This gland is in close relation with the hypothalamus and its centers, and there is probably a reciprocal influence on the gland and on many of the centers in this region. The influence of this hormone on the rate of water movement has been studied by Magnus and Schafer.[27] Schafer and Herring,[28] and by Abel and his associates;[29] its influence on the capillaries has been studied by Krogh and his associates.[30] The influence of this hormone on the rate of water movement is definitely shown in the slowing of water movement through the tissues after its administration in cases of diabetes insipidus. In accordance with the Kraus-Zondek conception of the action of drugs and hormones on the distribution of the electrolytes in the colloidal system of the protoplasm we must assume that the hormone of the posterior lobe of the hypophysis exerts its action on the physicochemical mechanism in the tissue membranes through which water moves by changing the electrolytic distribution there, and with it producing a change in the rate of water movement.

VIII. We have thus come to consider the mechanism which regulates the water exchange in the body as consisting of the following elements: (1) A regulating center in the interbrain closely connected with the centers for the regulation of sodium chlorid metabolism, other mineral exchange, protein, carbohydrate and fat metabolism, and other vegetative centers; (2) reservoir organs which take

up any excess of water from the blood, namely, the muscles and skin, especially their connective tissue, the liver, and possibly also the spleen; (3) barriers to the blood stream consisting of membranes in the tissues and the walls of capillaries through which the stream of water is regulated; (4) excretory organs, chief of which are the kidneys, but in addition the lungs, the skin and the intestines through which water is eliminated. All these organs, especially the connective tissue of the muscles and the skin, and the kidneys, constitute a functional unit regulated by the center.

Such regulation we conceive to be effected in the following manner: 1 Water absorbed from the alimentary tract produces a change in the water content of the blood. 2 The cells of the center in the hypothalamic region react to this change in the water content and respond with impulses to the organs constituting the functional unit to counteract the change in the water content of the blood. The impulses reach these organs by way of the vegetative nerves. 3 In addition to this nervous regulation the functional mechanism is under the continuous influence of the internal secretions of certain glands, chief of which are the intermediate and posterior lobes of the hypophysis. This gland again is under the regulating influence of the center in the hypothalamus.

4 The internal secretion of this gland as well as the vegetative nerves, affect the individual organs of the functional mechanism for water regulation through the electrolytes in the individual cells and through changes in the colloidal system of the cell. The change in the electrolytes is a change in the relation of certain electrolytes to one another and a change in concentration of the hydrogen and hydroxyl ions. With these changes there is a change in the intensity of the function of the cell and a change in the rate of the water movement.

The object of this whole mechanism is to maintain the normal water content of the organism, and especially the water content and volume of the blood. The latter is of paramount importance. A change in the intensity of the function of one organ of this mechanism must necessarily involve a corresponding change in the other organs if the object of the whole functional mechanism is to be maintained. The consideration of one organ of this mechanism as a separate entity entirely distinct of the others is therefore not possible. Nor can we consider the function of an organ of this mechanism apart from its regulating center and from the nervous impulses from this center. The consideration of changes in the electrolytes in a particular organ of this mechanism, whether the connective tissue of the skin and muscles, the capillaries, or the kidneys alone, without considering them as being continuously influenced by impulses from a center, is not permissible.

EDEMA

IX. With this conception of the manner in which the movement of water through the body is regulated we may consider the problem

of edema. We mean by edema the accumulation of fluid in the skin and subcutaneous tissue in such a manner that the fluid can be easily displaced by pressure on the skin, leaving a depression which soon disappears with the return of the displaced fluid. The fluid which has accumulated in the skin and subcutaneous tissue is not a part of the colloidal system of the protoplasm, but is an augmentation of the free fluid which is normally present between the colloidal systems and between the cells. This free fluid can be increased to a considerable degree without becoming noticeable except for the increase in weight, but when 5 to 6 liters have accumulated as free fluid in the various water depots, this becomes visible as edema. The questions we meet with are, first, how does it happen that so much water accumulates in the depots? and second, why does not the water move toward the blood stream to be excreted?

We know that the water from the depots can move toward the blood stream at various rates of speed. When water is ingested the mechanism for water exchange acts at once, the ingested water goes from the blood stream into the tissues, returns to the blood stream and is excreted by the kidneys. When much water is ingested the rate of movement of the water is rapid; when no water is ingested, the rate is slow. This is shown by the urine output, which is increased in the first case and diminished in the second. The blood volume remaining within normal limits in either case, the excess of water to be excreted must move at a greater rate. When, as in edema, water persists in the depots, the rate of movement through the tissue barriers to the blood stream is evidently diminished. We have said that the rate of movement of water through such barriers is dependent upon the electrolytic constellation in them. We must assume then that a change has occurred in the physicochemical regulation, that is, in the distribution of electrolytes in the tissue barriers where the rate of water movement is diminished. When the fluid keeps coming into the depots at the regular rate of flow, but the rate of flow from the depots to the blood stream is diminished, the free water in the depots must necessarily be increased. When the increase has reached a certain degree the water becomes visible as edema.

We must therefore consider general edema, that is, the accumulation of free fluid in the water depots of the body to a visible extent, as the result of a discrepancy between the more rapid rate of movement of water from the blood to the tissues and the slower rate of movement in the opposite direction. Whenever such a discrepancy occurs edema must necessarily result.

Edema results also in some local area alone when such an area is inflamed, such as occurs in local myositis or cellulitis. In this case the local discrepancy in the rates of water movement can be assumed to be due to a local change in the electrolytes in that areas as a result of the inflammation.

When the edema is general such as occurs in cardiac failure, in acute nephritis, or in chronic starvation, the diminution in the rate of water movement over the entire body must be the result of a change in the electrolytic distribution in the entire peripheral mechanism for water exchange, namely, the muscles, skin, liver and kidneys. Such a widespread change involving the entire mechanism could possibly be produced by a toxic substance which circulates in the blood stream and thus reaches the entire mechanism. This is perhaps the case in the edema found in a generalized myositis, in the edema which occurs in trichinosis, in the edema which sometimes occurs in arsenic poisoning, and in that of experimental uranium poisoning. But we know of no poison circulating in the blood stream which may affect all the tissues in cases of edema of cardiac failure, of renal disease, or of chronic undernutrition. Here we must assume that a change in the electrolytes responsible for the slowing in the rate of water movement is produced reflexly by way of the central nervous control acting through the vegetative nerves or through hormonal influences, or in both ways. In diabetes insipidus such a general change produced by the regulatory center results in an increase in the rate of water movement. It is, therefore, easy to understand that a change of regulation in the opposite direction would produce a slowing in the rate of water movement. If there is thus a discrepancy between the rate of flow to the tissues and the rate of flow from the tissues, a generalized edema must result after a certain amount of water has accumulated.

X. The question which confronts us now is: under what conditions is such a regulatory change in the mechanism brought about? We have said that the organism has means of maintaining the constancy of the internal milieu. It is particularly the volume and water content of the blood which the organism continuously maintains within certain limits and which vary but slightly even in pathologic conditions. If the mechanism we have discussed serves such a purpose then it must come into play whenever the normal water content of the blood is endangered. This is actually what occurs. We know that when the body is deprived of water all the free water in the tissues will be drained into the blood stream before the blood begins to lose its water, while at the same time the kidneys shut down to prevent any loss of water through them, even to complete anuria. In severe diarrheas, such as occur in cholera, the tissues become completely dry and anuria results in an attempt on the part of the organism to keep the water in the blood.

The opposite also occurs. Under certain conditions there is danger that the water content of the blood will become unduly increased. If the mechanism for the regulation of water exchange is to fulfill its purpose it must immediately regulate the rate of water movement to the blood stream in such a manner that an undue increase in the water content of the blood is prevented. The conditions in which

such a threatened increase in the water content of the blood occurs are cardiac failure and acute diffuse nephritis.

In cardiac failure there is a slowing of the blood stream and the blood accumulates in the venous system. As the blood accumulates it is taken up by the various organs, which become passively congested. A great deal of blood can be removed in this manner by the liver, the spleen and the capillaries of the skin. The importance of the latter has been shown by Wollheim.[31] The kidneys also become congested and the glomeruli are filled with blood. The result of glomerular overfilling is a diminution in the flow of blood through them, a diminution in the output of urine and, of course, a diminution in the excretion of water. When the limit of congestion is reached, then the mechanism for water exchange must come into play and adapt the rate of water movement from the tissues to the blood stream to the rate with which it leaves the body through the regular channels, so that the water content of the blood is maintained within the normal limits.

Impulses reaching the central regulation of the mechanism for water exchange cause reflexly, by way of the nerves or homones, or both, a change in the electrolytic distribution throughout all the effector organs of the mechanism. The result is a slowing in the rate of water movement through the tissue barriers to the blood stream. As the intake of water remains normal and is quickly removed after ingestion, the free water in the depots is quickly increased and soon becomes visible as edema.

In acute diffuse nephritis there is also danger that the water content of the blood may become unduly increased. In this disease all the glomeruli of both kidneys are affected. They are filled with an exudate consisting of leukocytes and endothelial cells, and with a hyaline plasma. Practically no red blood corpuscles pass through them and, depending upon the severity of the inflammation, a more or less thin trickle of plasma passes through the capillaries of the glomeruli. The result is a diminution in the output of urine and, of course, of water. The water content of the blood would necessarily increase if the water kept moving through the tissues at the same rate of speed as before. The blood volume, however, remains normal. We must therefore assume that there is a slowing in the rate of water movement from the depots to the blood stream corresponding to the rate with which water is lost from the body through the diseased kidneys and through the extrarenal channels. There is therefore produced reflexly through the central regulation a generalized change in the electrolytic distribution in all the tissue membranes through which water moves. Water taken in as usual is quickly removed to the depots. The diminution in the rate of removal from the depots results in an increase there in the free water, which soon appears as edema.

Thus we have two conditions in which a threatened increase in

the water content of the blood is prevented by the proper adaptation of the mechanism for water exchange. Such an adaptation can only be brought about through a central regulation.

In this connection it is important to remember the influence of the sodium chlorid content of the free water in the depots. Sodium chlorid passes from the blood to the tissues and in the opposite direction in solution. It is clear that when the rate of water movement is diminished the rate of movement of sodium chlorid is also diminished. When edema occurs, the salt contained in the food, absorbed into the blood stream, and passed into the tissues, is prevented from returning to the blood stream by the slowing in the rate of water flow. As its concentration increases it draws more water to it and thus helps to increase the extent of the edema.

We have so far assumed that the volume and water content of the blood remain within the normal limits in both the conditions where the mechanism for water regulation prevents an undue increase. That the blood volume is actually within the normal limits has been shown by the studies of Bock,[32] Linder, Lundsgaard, van Slyke and Stillman,[33] Seyderhelm and Lampe,[34] Schmidt,[35] Brown and Rowntree.[36]

XI. We have so far made an attempt to explain the edema which appears when the constancy of the water content of the internal milieu is threatened. There occur, however, excessive accumulations of water in the tissues when the constancy of the water content of the internal milieu is not threatened. Such accumulations of water are seen in the edema of chronic undernutrition, of severe diabetes, in chronic wasting disease and in myxedema. In all these conditions the water content of the blood is not disturbed, actually it is within the normal limits, and yet the rate of water movement from the tissues to the blood has become slower compared to the rate of flow of water from the blood stream to the tissues. For only through such a discrepancy can a sufficient amount of free water accumulate in the tissues to become visible as edema. As the edema is general, there must have occurred a change in the whole mechanism for water movement, and, as we have said before, such a general change must occur through the central regulatory mechanism. We know of no toxic substance which circulates in the blood in chronic undernutrition and which may produce a change in the barrier membranes without the intervention of the central regulatory control. Evidently, for some reason, such a change does occur. Under what conditions is it brought about?

When we examine the diseases mentioned, namely, chronic undernutrition, wasting diseases, severe diabetes with edema and myxedema, we find certain factors common to all. In all of these there is a diminution in intensity in a number of vegetative functions. There is a diminution in the state of nutrition and in the basal metabolic rate. Typical is the state of chronic undernutrition as

it was observed in the cases of war edema. We find here a diminution in the metabolic rate, in the blood pressure, in the pulse rate, in the amount of protein in the blood, even in the body temperature. There is thus a diminution in rate in a number of vegetative functions. Physiologically a decrease in practically all vegetative functions occurs periodically in the hibernating animal. Basal metabolic rate, circulation, blood pressure and respiration rate, are all diminished during hibernation. Urination practically ceases and the rate of water movement through the tissues is at a minimum. We know that all these vegetative functions have a central control in the nervous system and it is difficult to see how such a general lowering of all the functions can be brought about in the hibernating animal except through the intervention of the central regulatory apparatus.

It is therefore logical to assume that the depression of a number of vegetative functions in chronic undernutrition is similarly brought about by changes in the regulatory control. The purpose is the conservation of the chronically undernourished organism. Lusk[37] points out that the reduction in the basal metabolism in chronic undernutrition affords a factor of safety for the conservation of the body.

We may now take a step further and logically assume that with such a regulatory change in other vegetative functions there is also a regulatory change in the rate of water movement. This, like the rate of other functions has become slower. The slowing is particularly seen when an extra load of water and salt is given. Jansen,[38] and Schittenhelm and Schlecht[39] studied the cases of war edema. From their studies it is evident that when large amounts of water and salt are given to cases of chronic undernutrition there is evidence of a diminution in the rate of water movement from the tissues to the blood stream. With the intake of large amounts of water and salt which promptly move into the water depots, there is an increase in the free water there which soon appears as edema.

Our conception then of the formation of edema in chronic undernutrition—and that includes the undernutrition due to a faulty diet, that of severe diabetes, and of chronic wasting diseases—is as follows: with the progress of the undernutrition there is a depression of many of the vegetative functions as a result of central regulatory influences. Water movement through the body, being a vegetative function the central regulation of which is closely associated with that of other fundamental functions, especially with that of metabolism, is similarly depressed. As the water content of the blood remains within the normal limits, the intake of large amounts of water and salt is necessarily followed by an increase in the amount of water in the tissues which soon becomes visible as edema.

XII. In addition to the forms of edema which we have discussed there occur cases of edema without any apparent cause, that is, without any cardiac failure or renal disease, and without chronic undernutrition. I have seen several such cases and have reviewed the reported cases elsewhere.[40] The cases, especially those which have been studied more thoroughly, seem to have certain things in common. None of these patients suffered from any cardiac or renal affection or from chronic undernutrition which would cause edema. They all had edema which was more or less generalized, with a diminution in the urinary output. In those cases which were properly studied there was a diminution in the free hydrochloric acid of the stomach or a total absence of it, a more or less normal output of an added amount of water, and a retention and delayed excretion of an added amount of sodium chlorid. In some cases there was also a diminution in the protein content of the blood plasma. There are no studies recorded concerning the blood volume in these cases, but we are probably correct if we assume that the blood volumes were within the normal limits.

We may, therefore, agree with the authors of these reports that the edema is the result of a disturbance in the sodium chlorid exchange. The rate of movement of sodium chlorid through the tissues and membranes is diminished. The diminution in the rate of movement affects the sodium chlorid in all the regions of the body and is therefore most likely to be the result of a disturbance in the center of regulation.

XIII. With this conception of edema the directions for its treatment stand out clearly. The treatment of the fundamental disease of which edema is the symptom comes first. This is the case in cardiac failure. In acute diffuse nephritis we have no means to influence the pathologic process in the kidneys directly.

When we come to treat the symptom of edema, there are certain principles which we can follow:

1. To diminish the intake of water below that of the output, no matter how small, as long as there is no anuria. When the intake is diminished below the output the water lost from the blood must be made good from the water in the tissues if the blood volume is to remain normal.

2. The total or almost total elimination of sodium chlorid from the food. The loss of sodium chlorid from the blood by way of the urine must be made good from the salt in the tissues which passes into the blood stream and takes water with it.

There are no direct means of influencing the regulatory center for water exchange itself. But when this is primarily responsible for the slowing in the rate of water movement the basal metabolic rate also is usually slowed, as in chronic undernutrition. When the basal metabolic rate is increased the rate of water movement is also increased. We have then,

3. To stimulate the rate of oxidative processes in the cells whenever it is found to be diminished.

For this purpose we have two means at hand: first, a proper diet, especially rich in protein, such as has been suggested by Epstein[41] in cases of lipoid nephrosis; and second, the hormone of the thyroid gland, which has been introduced into the treatment of edema by Eppinger.[36]

When, in spite of the limitation of water and salt intake, the edema cannot be controlled we have at our disposal diuretics as follows:

The purine substances, caffein, theobromin, theophyllin, and their derivatives.

The mercury compounds, calomel, novasurol and salyrgan.

Calcium chlorid and ammonium chlorid.

Urea.

The action of the purine derivatives and of the mercury compounds we assume to be on the kidneys and on the tissue barriers through which water moves. In accordance with our ideas concerning the similarity of the action of drugs and poisons and of nerves on the electrolytes of the colloidal system of the protoplasm, it is logical to assume that the action of these drugs is on the tissue barriers through which water moves. In all probability a change in the electrolytes of the tissues is brought about by these drugs, the result of which is an increase in the rate of water movement through them. It is clear that these drugs should not be used when an acute inflammatory exudate blocks the glomerular capillaries through which the excess of water must be removed.

The diuretic action of the acid-producing salts, such as calcium chlorid and ammonium chlorid, is due to the excess of acid radicals in the body, which must be excreted in solution, and the excretion thus carries with it a certain amount of water.

The diuretic action of urea is primarily in the kidneys, and is due to its not being reabsorbed in the tubules; it thus prevents a certain amount of water from being reabsorbed. Whether it also has an effect on the tissues is not known.

Summary. We have thus come to the understanding that in every case of general edema there is a slowing up in the rate of movement of water from the depots through the tissue barriers to the blood stream. With the normal water and salt intake and their rapid removal from the blood into the tissues, the free water there is rapidly increased. When a certain amount of water has accumulated it becomes visible as edema. The slowing is the result of a central regulatory change and affects the constellation of electrolytes in the tissue barriers through which the water moves to the blood and lymph streams. This slowing is produced, first, whenever the water content of the blood threatens to be unduly increased, as in cardiac failure, or in acute diffuse nephritis; second, when the

change is primarily in the regulatory center, along with the depression of other vegetative functions, especially of the basal metabolic rate. This is the case in chronic undernutrition and in chronic wasting disease. Third, when there is a primary disturbance in the central regulation for the control of sodium chlorid in the body. This is the case in certain cases of edema without cardiac or renal diseases, and without chronic undernutrition.

REFERENCES.

1. Haldane, J. S.: The New Physiology, The Harvey Lectures, Series XII, J. B. Lippincott Company, 1916–1917, p. 25.
2. Bernard, Claude: Leçons sur les phénomenes de la vie, Paris, 1878, **1**, 113.
3. Marx, H.: Untersuchungen über den Wasserhaushalt (1 Mitteilung), Die Blutberdünnung nach Flüssigkeitsaufnahme, Klin. Wchnschr., 1925, **4**, 2339. Untersuchungen über den Wasserhaushalt (II Mitteilung); Die psychische Beeinflussung des Wasserhaushaltes, Klin. Wchnschr., 1926, **5**, 92. Untersuchungen über den Wasserhaushalt (III Mitteilung): Über die Austauschvorgänge zwischen Blut und Gewebe bei Gesunden und Kranken, Deutsch. Arch. f. klin. Med., 1926, **152**, 354.
4. Magnus, R.: Über die Veränderung der Blutzusammensetzung nach Kochsaltzinfusion und ihre Beziehung zur Diurese, Arch. f. exper. Pathol. u. Pharmakol., 1900, **44**, 68.
5. Engels, W.: Die Bedeutung der Gewebe als Wasserdepots, Arch. f. exper. Pathol. u. Pharmakol., 1904, **51**, 346.
6. Wahlgren, W.: Über die Bedeutung der Gewebe als Chlordepots, Arch. f. exper. Pathol. u. Pharmakol., 1909, **61**, 97.
7. Tashiro, N.: Über Änderungen im Wassergehalte der quergestreiften Muskulatur als Folge der Störungen des Wasserhaushaltes von Kaninchen, Naunyn-Schmiedeberg's Arch. f. exper. Pathol. u. Pharmakol., 1926, **111**, 218.
8. Baer, B.: Über die Bedeutung der quergestreiften Muskulatur für de Regelung des Wasserhaushaltes bei peroraler Wasser- und Salzdarreichung, Naunyn-Schmiedeberg's Arch. f. exper. Pathol. u. Pharmakol., 1927, **119**, 102.
9. Lamson, P. D. and Roca, J.: The Liver as a Blood Concentrating Organ, J. Pharmacol. and Exper. Therap., 1921, **17**, 481.
10. Pick, E. P.: Wasser- und Mineralstoffwechsel in ihren Beziehungen zu Verdauungs- und Stoffwechselkrankheiten, Verhandl. d. Gesellsch. f. Verdauungs- u. Stoffweichselkrankh., 1927, **6**, 125.
11. Barcroft, J.: Some Recent Work on the Function of the Spleen, Lancet, 1926, **210**, 544.
12. Zondek, S. G.: Die Electrolyte, Julius Springer, Berlin, 1927.
13. Reid, E. W.: Transport of Fluid by Certain Epithelia, J. Physiol., 1900–1901, **27**, 436.
14. Wertheimer, E.: Über irreziproke Permeabilität, Pflüger's Arch. f. d. ges. Physiol., 1923, **199**, 383; Über die Quellung geschichteter Membranen und ihre Beziehung zur Wasserwanderung, Pflüger's Arch. f. d. ges. Physiol., 1925, **208**, 669; Weitere Untersuchungen an lebenden Membranen, Pflüger's Arch. f. d. ges. Physiol 1925, **210**, 527.
15. Mond, R.: Untersuchungen am isolierten Dünndarm des Frosches, Pflüger's Arch. f. d. ges. Physiol., 1924, **206**, 172.
16. Hoffmann, A., and Wertheimer, E.: Eine nervöse Regulation im Wasserhaushalt, Pflüger's Arch. f. d. ges. Physiol., 1927, **217**, 138.
17. Eckhard, C.: Zur Deutung der Entstehung der vom vierten Ventrikel aus erzeugbaren Hydrurie, Ztschr. f. Biol., 1903, **44**, 407.
18. Aschner, B.: Über die Funktion der Hypophyse, Pflüger's Arch. f. d. ges. Physiol., 1912, **146**, 1.
19. Camus, J. and Roussy, G.: Hypophysectimie et polyurie expérimentales, Compt. rend. Soc. de biol., 1913, **75**, 483; Polyurie expérimentale permanente (Diabète insipide), Compt. rend. Soc. de biol., 1920, **83**, 764.
20. Houssay, B. A.: Aur la polyurie soidisant hypophysaire, Compt. rend. Soc. de Biol., 1918, **81**, 381.
21. Leschke, E.: Beiträge zur klinischen Pathologie des Zwischenheirns, Ztschr. f. klin. Med., 1919, **87**, 201.

22. Bailey, P. and Bremer, F.: Experimental Diabetes Insipidus, Arch. Int. Med., 1921, **28**, 773.
23. Curtis, G. M.: The Production of Experimental Diabetes Insipidus, Arch. Int. Med., 1924, **34**, 801.
24. Pohle, E.: Einfluss des Nervensystems auf die Osmoregulation der Amphibien, Pflüger's Arch. f. d. ges. Physiol., 1920, **182**, 215.
25. Jungmann, P. and Bernhardt, H.: Experimentelle Untersuchungen über die Abhängigkeit der Osmoregulation von Nervensystem, Ztschr. f. klin. Med., 1924, **99**, 84.
26. Eppinger, H.: Zur Pathologie und Therapie des menschlichen Ödems, Julius Springer, Berlin, 1917.
27. Magnus, R. and Schafer, E. A.: The Action of Pituitary Extracts upon the Kidney, J. Physiol., vol. **27**, Proc. Physiol. Soc., 1901, p. ix.
28. Schafer, E. A. and Herring, P. T.: The Action of Pituitary Extracts upon the Kidney, Proc. Roy. Soc. London, Series B., 1906, **77**, 571.
29. Abel, J. J.: Physiological, Chemical and Clinical Studies on Pituitary Principles, The Harvey Lectures, Series XIX, J. B. Lippincott Company, 1923–1924, p. 154.
30. Krogh, A.: The Anatomy and Physiology of the Capillaries, New Haven Press, New Haven, 1922.
31. Wollheim, E.: Zur Funktion der subpapillären Gefässplexus in der Haut, Klin. Wchnschr., 1927, **6**, 2134.
32. Bock, A. V.: The Constancy of the Volume of Blood Plasma, Arch. Int. Med., 1921, **27**, 83.
33. Linder, G. C., Lundsgaard, C., Van Slyke, D. D., and Stillman, E.: Changes in the Volume of Plasma and Absolute Amount of Plasma Protein in Nephritis, J. Exp. Med., 1924, **39**, 921.
34. Seyderhelm, R. and Lampe, W.: Die Blutmengenbestimmung und ihre klinische Bedeutung, Ergebn. d. inn. Med. u. Kinkerheilk., 1925, **27**, 245.
35. Schmidt, W.: Blutmengen-Bestimmungen bei Nieren- und Herzkranheiten, Ztschr. f. d. ges. exper. Med., 1927, **58**, 276.
36. Brown, G. E. and Rowntree, L. G.: Blood Volume in Edema of Glomerular Nephritis and Nephrosis, Arch. Int. Med., 1928, **41**, 44.
37. Lusk, G.: The Physiological Effect of Undernutrition, Physiol. Rev., 1921, **1**, 523.
38. Jansen, W. H.: Die Ödemkrankheit, Deutsch. Arch. f. klin. Med., 1920, **131**, 144.
39. Schittenhelm, A. and Schlecht, H.: Die Ödemkrankheit, Julius Springer, Berlin, 1919; reprinted from Ztschr. f. d. ges. exper. Med., 1919, **9**, 1.
40. Elwyn, H.: Edema and Its Treatment, p. 130, The Macmillan Company, New York, 1929.
41. Epstein, A. A.: Concerning the Causation of Edema in Chronic Nephrosis, Am. J. Med. Sci., 1917, **154**, 638.

GASTRIC HEMORRHAGE DUE TO FAMILIAL TELANGIECTASIS.

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A cursory survey of the literature disclosed records of 3 cases of recurrent rectal hemorrhage, one of oral bleeding and one of hematemesis, which had been accompanied by cutaneous telangiectases. Wilson[1] gave us the first recorded instance of rectal bleeding from telangiectases in 1896; Fox[2] recorded a case in 1908, where recurrent rectal hemorrhage was an annoying symptom; Phillips[3] in 1908

cites the case of an extensive telangiectasis of the skin and mucous surface of the mouth with hemorrhages from the pharynx, and possibly from the stomach. Hutchinson and Oliver's[4] patient experienced recurrent rectal hemorrhage and hemorrhage from other mucous membranes; and Pringle[5] in describing his case alludes to recurrent attacks of vomiting blood. Gastric hemorrhage, in the absence of pain and other gastrointestinal symptoms, has been the outstanding clinical feature in the 3 case records here delineated.

Familial epistaxis and familial telangiectasis are terms seldom used but known to otolaryngology; whereas telangiectasis has not been employed in connection with painless hemorrhage of either gastric or rectal origin.

The 3 private cases furnishing the clinical subject matter for this report, each had telangiectases of the skin and mucosæ, as well as recurrent hemorrhages from both the stomach and the rectum. One of these patients was studied at laparotomy and another died from gastric hemorrhage. In each instance the history indicated other members of the same family, or near relatives who had experienced similar attacks of bleeding from mucous surfaces. The familial etiologic nature of the disease is evidenced in the report of my cases, and in all records cited from the literature.

Painless gastric hemorrhage, calls for a careful inquiry regarding the existence of recurrent mucous bleedings among other members of the family. Moreover, persons suffering from recurrent epistaxis may also bleed from other mucous membranes.[6]

Characteristic of familial gastric and rectal hemorrhage are: (*a*) the blood clotting time is within normal limits; (*b*) the number of blood platelets per cubic millimeter varies between 250,000 and 400,000; (*c*) following large hemorrhages, the blood findings are those of secondary anemia, while nucleated red blood cells are occasionally present; (*d*) patients recover rapidly following seemingly large hemorrhages; (*e*) cases do not bleed extraordinarily after surgical operations; (*f*) and the other symptoms suggestive of gastric lesions are conspicuously absent.

Each of the patients here reported lived to over fifty years of age, and each had been a victim of recurrent gastric hemorrhage since early life. One of these patients in addition to giving a definite history of familial nasal, gastric and rectal bleeding, is also the father and the grandfather of victims of recurrent nosebleed. In Cases I and II, telangiectases detected on the gastric mucosæ were the sites of hemorrhage.

Case Reports. CASE I.—Male, aged thirty-two years, employed by the city fire department, was treated by me during a period of three years (ending in 1914), for recurrent attacks of gastric hemorrhage. Upon several occasions he passed considerable blood by rectum. Proctoscopic examination failed to reveal any evidence of hemorrhoids, or other pathology of the rectal mucosa. There were small telangiectases located on the face, scalp,

chest and lip. A tentative diagnosis of gastric ulcer, without pain or tenderness, was ventured. Hemorrhage from the stomach was first noted when a boy and while attending school. He was compelled to refrain from taking an active part in school athletics, because he occasionally vomited blood after strenuous exercise.

Family History. The patient's father had suffered from two severe attacks of gastric hemorrhage; and had also experienced the vomiting of a small amount of blood one or more times each year since a young man. The father was at this time sixty-four years of age and a sufferer from apoplexy; he vomited blood twice during the last year of his life, and died from cerebral hemorrhage.

Clinical Observation. Physical examination failed to detect anything abnormal except the small cutaneous telangiectases previously mentioned. The heart was normal; blood pressure, systolic 128, diastolic 80. The pulse was of good volume, regular and not influenced abnormally by exercise. Examination of the oral and nasal cavities gave negative findings.

While under my observation, he vomited blood seven times and reported rectal bleeding often. The quantity of blood ejected was never large, he ordinarily vomited from 2 to 4 ounces of blood-stained material. Chemical examination of this vomitus showed it to be acid in reaction, contained decomposed blood in certain instances, whereas two of the specimens showed many red blood cells and large clots. The attacks of vomiting blood were experienced twice after the too liberal imbibition in rich food and alcoholic beverages. During routine study, he was given an Ewald meal, the gastric content recovered and found to be normal. It was not possible at any time during this clinical observation, to elicit tenderness over the abdomen, and the patient contended that he never experienced discomfort either before, during or after the gastric hemorrhages.

Roentgen-ray studies made at the Medico-chirurgical Hospital showed the stomach and intestine to be normal.

Laboratory Studies. The red blood cells were 3,710,000; leukocytes, 8,400 per c.mm.; hemoglobin, 76 per cent. A differential leukocyte count gave polymorphonuclears 68, small lymphocytes 23, large lymphocytes 5, eosinophiles 2, basophiles 1 and transitionals 1. Coagulation time (Boggs' coagulometer) was three minutes and fifteen seconds. The feces were examined upon several occasions for ova, and parasites with negative findings. Reaction of the feces for occult blood was positive.

While on duty, and attending a fire, he was compelled to work for several hours without his regular food or sleep. During this strenuous exertion he fainted and was brought to the hospital. Pursuant with a record of recurrent gastric hemorrhages and his present state of shock, I consulted with the late Professor Ernest LaPlace, who performed a laparotomy.

Findings. The visceral peritoneum appeared normal, except for a telangiectatic area, size of a pea, located upon the anterior surface of the gall bladder. The stomach contained a large volume of blood. Well toward the cardiac portion of the stomach, were two areas where the organ appeared to be unusually vascular. The stomach was opened in search of the bleeding site. The two hypervascular areas mentioned were pronounced by the surgeon to be small nevi, each being about one-fourth of an inch in their lesser diameter; and numerous bloodvessels were visible about these sections. Upon sponging these nevus-like areas, it was found that one of them bled after slight pressure, but to the naked eye, there was no actual erosion of either arteries or veins.

The operative procedure was the elective one of ligating an artery that supplied these highly vascular sections. The patient made a slow recovery and when last seen, five years after the operation, claimed he had not suffered an attack of gastric hemorrhage since operation.

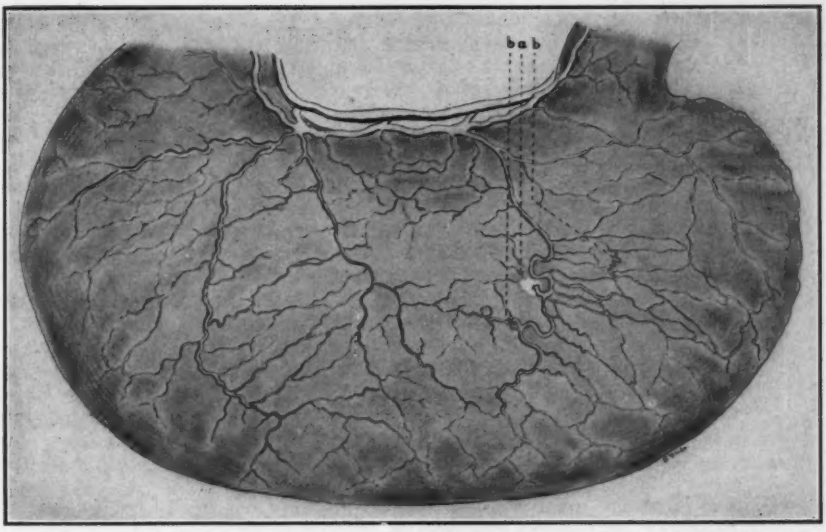

FIG. 1.—The stomach was opened along the greater curvature. Sketch shows venous distribution on the posterior wall. *a*, Lesion from which fatal hemorrhage occurred. *b*, *b*, two sections of the mucosa, showing extreme venous vascularity (these resembled telangiectases surrounded by minute plexuses of vessels). It was impossible to distinguish between small arteries and veins at these potential sites of bleeding.

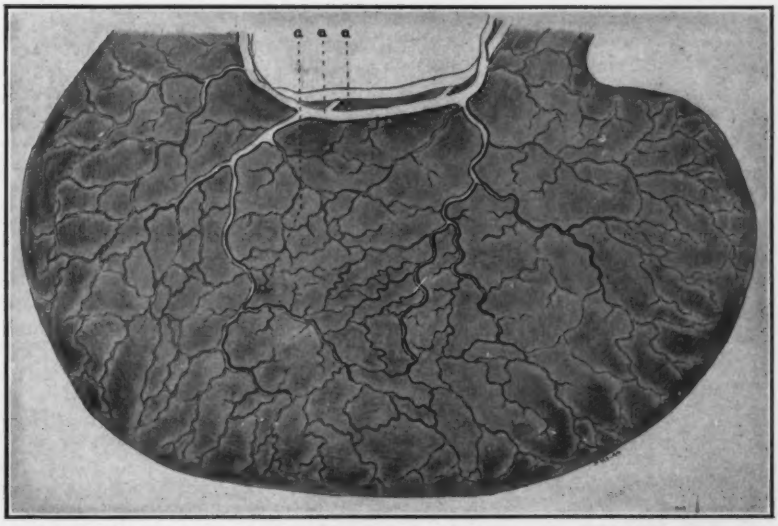

FIG. 2.—Sketch of venous supply of anterior wall of stomach (viewed from the peritoneal surface), while stomach was held in front of a strong light. *a*, *a*, *a*, Healed sites of previous hemorrhage. No sensation of thickening was detected, and they did not resemble the usual healed ulcer.

CASE II.—E. D., female, aged seventy years, admitted to the Woman's College Hospital, October 30, 1929, after vomiting 8 ounces of blood-stained fluid. She had had "stomach trouble" for years; recurrent attacks of faintness, usually mild but often severe enough to necessitate her sitting from one-half to several hours. Nausea was present, but vomiting rarely occurred. She had noticed recurrent attacks of bleeding from the rectum since early girlhood. The loss of blood through rectal hemorrhages did not impair her health. Four children are living, labors were normal.

Family History. Her mother died at seventy years, but was never a victim of attacks of hemorrhage. A maternal aunt suffered from recurrent attacks of nasal hemorrhage. A sister of the patient died at the age of fifty-six from repeated painless gastric hemorrhages. A brother died of apoplexy; three brothers living.

Present Illness. The patient enjoyed health until March, 1928, when, in the absence of other symptoms, she vomited about 2 quarts of blood-stained liquid. She was confined to the hospital for twenty-six days. She made an uneventful recovery, gained steadily in strength and weight. The hemoglobin rose from 30 to 70 per cent. Symptoms referable to stomach trouble were absent until October 30, 1929, when she entered the Woman's College Hospital. Slight chills and fullness in the stomach antedated vomiting, but pain was absent.

Physical Examination. A well-developed, white woman, weak and pale. A soft systolic murmur was heard at the apex and transmitted to the left axilla. Cardiac sounds were regular, but the muscle tone was poor. Gurgling sounds were active over the abdomen. A large scar covered the superior portion of abdomen, back and both arms, due to a burn by gas forty years ago. Two hours after admission (9 P.M.) the patient vomited 15 ounces of bright blood, and a half hour later, she again vomited 2 ounces of blood. Hemostatic serum (2 cc.) was given every two hours for 3 doses.

There was one small angiomatous patch, 0.5 mm. in diameter on right eyelid at junction of the skin and mucous membrane. There were eight other telangiectases located on the neck, chest, abdomen, and right thigh. On the outer surface of right thigh near its center there were several areas of dilated bloodvessels about 1½ inches in width and 2½ to 3 inches in length, the longer measurements being nearly parallel with the femur. Inside of the right thigh were a few dilated vessels of the skin, and several telangiectases on the left leg.

The urine was amber in color, acid, specific gravity 1020, and contained a trace of albumin; otherwise negative.

On account of extensive scaring from previous burns, a successful transfusion was impossible. On admission the blood examination revealed hemoglobin, 60 per cent; erythrocytes, 3,370,000; leukocytes, 6,700; clotting time, three and a half minutes. Subsequent blood examinations revealed a rapid decrease in both erythrocytes and hemoglobin. Blood platelets numbered 340,000.

Four days after admission the patient suddenly became nauseated and vomited 4 ounces of blood, followed by sweating, chills, weak rapid pulse and restlessness. She died on the fifth day following severe gastric hemorrhage.

Pertinent Autopsy Findings. The esophagus was normal. The stomach contained 1 pint of blood and a large clot. On the posterior surface, 5 cm. from the esophageal opening, was an erosion 0.5 cm. in diameter, the center of which was occupied by a vessel whose mouth was plugged by a clot. By holding the stomach against the light it was seen that this vein communicated with a large branch of the coronary veins (Fig. 1). Toward the lesser curvature (on the anterior wall) were three minute white scars smaller than a pin's head (Fig. 2). These scars were situated along the course of

the veins. Each scar was located on a portion of highly vascular mucosa. When held up to the light, a minute yellow-white thickening could be seen surrounded by a thin white halo. None of the scars, or the lesion at site of hemorrhage felt thickened at autopsy, but after hardening the organ, it was possible to feel slight thickening of these scars with the ungloved hand. The intestines were filled with thick, tarry blood. The upper part of the small intestine was discolored red, the lower part reddish black and the colon black from the presence of blood.

CASE III.—Male, age sixty years, first seen by me in 1925.

Chief Complaint. Obstinate constipation, recurrent attacks of tenderness over the upper abdomen, followed by nausea and faintness. Gastric distress at times became severe and the pain was only relieved by the taking of food. He had repeatedly vomited during these attacks and the vomitus usually contained some blood. It was his custom to pass a small amount of blood from the bowel the day following these seizures.

Family History. The mother, a maternal grandfather and a maternal uncle and the patient's sister had suffered from recurrent attacks of nosebleed. The patient has a son and a grandson who are also sufferers from familial telangiectasis, both of whom experienced their first attack of nasal hemorrhage at about the tenth year of age. The inherent tendency to transmit the pernicious defect of telangiectasis is well exemplified by this patient.

Physical Examination. Physical examination revealed nothing of clinical importance except the presence of small telangiectases situated on the neck, trunk and nasal mucosa. He had received treatment (cauterization) for "spider nevi" located on the nasal mucosa.

Conclusion. Familial telangiectasis is the etiologic factor in a definite class of hemorrhage, which takes place in the presence of normal physiologic responses by both the capillary and venous blood. Recurrent gastric hemorrhages were experienced during early life by each of the 3 cases studied; and attacks of hemorrhage were often accompanied by brief periods of syncope. Judging from the small number of case reports available, familial telangiectasis does not shorten the span of life or inhibit development. Familial gastric hemorrhage has been observed, in persons who have also experienced recurrent attacks of hemorrhage from other mucous surfaces. The vascular defects common to familial hemorrhages from the mucous membranes are to be found among other members of the same family and in their near relatives. The tendency to familial hemorrhage is transmitted by both maternal and paternal parent to offspring.

REFERENCES.

1. Wilson: J. Cutan. Med. and Dis. Skin, 1869, **3**, 198.
2. Fox: Brit. J. Dermat., 1908, **20**, 145.
3. Phillips: Proc. Roy. Soc., London, 1908, **1**, 64.
4. Hutchinson and Oliver: Quart. J. Med., 1916, **9**, 67.
5. Pringle: Proc. Roy. Soc. Med., London, 1912, **6**, 129.
6. Boston: Med. Times, 1930, **58**, 68.

THE EFFECT OF LIVER EXTRACT ON THE BLOOD OF NORMAL PERSONS.*

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That the ingestion of liver extract may cause in a normal person a prompt and striking rise in the red blood cell count accompanied by symptoms and signs of polycythemia is a fascinating problem for speculation. Watkins, Johnson and Berglund[1] observed a rise in the red blood cell count to as high as 7,800,000 and the simultaneous occurrence of symptoms of headache, epistaxis, vertigo and with particularly acrocyanosis. They suggest that the action of the unknown substance or substances contained in the extract which are effective in allowing an increase of red blood cells in pernicious anemia act in the manner of a stimulant for the maturation and discharge of normal red blood cells. Inasmuch as these observations have not been corroborated up to the present time, the following studies were made.

Procedure. Following control studies, during which the normal blood values were determined, the contents of eight vials of a potent liver extract,† the equivalent of 800 gm. of liver, were ingested daily for a period of fourteen days by four normal young men. During the period of observation each took his customary normal diet.

In the observation period red blood cell counts were made from blood obtained from an ear-lobe puncture, twice daily, at approximately 10 A.M. and 3 P.M. Counts were made from two United States Bureau of Standards standardized pipettes each time and the average of the two counts recorded. The reticulocytes were counted in smears of the blood made at the same time and stained with brilliant cresyl blue.

Before treatment was begun, and at weekly intervals thereafter, observations were made on venous blood as follows: The percentage of blood hemoglobin (Sahli), red blood cell count, the total cell volume by hematocrit, individual cell volume,[2] blood iron,[3] icteric index[4] and the mean red blood cell diameter by measurements.

Observations. The reticulocyte response was as follows: On the fifth day in each subject there occurred a distinct increase from

* This study was aided by a grant from the Proctor Fund of the Harvard Medical School for the study of chronic disease.

† Supplied by Eli Lilly & Co.

control values reaching 3, 1.3, 1.4 and 1.1 per cent respectively. Although the percentage increase is small, it is to be noted that on the basis of 5,000,000 circulating red blood cells per cubic millimeter, this would give actual reticulocyte figures of between 150,000 and 55,000 per c.mm. These figures would compare with a 15 per cent reticulocyte rise in a patient with 1,000,000 red cells per c.mm., as in severe pernicious anemia. The rise was transitory, persisting for from one to three days, following which the values decreased apparently to below the control figures.

TABLE I.

Time.	Red blood cells per c.mm.	Hemoglobin (cap.).	Hemoglobin (ven.).	Reticulocytes, per cent.	Hematocrit, per cent of cells.	Individual cell volume	Blood iron.	Mean diameter, microns.
A.M. . .	5,050,000(V)	..	113	0.7	46.5	9.2	46.14	7.62
P.M. . .	4,440,000	118	..	0.6				
A.M. . .	4,890,000	113	..	0.6				
P.M. . .	5,010,000	114	..	0.5				
A.M. . .	5,040,000	113	..	0.4				
A.M. . .	...	Liver extract started.						
A.M. . .	5,060,000	119	..	0.4				
P.M. . .	5,200,000	115	..	0.6				
A.M. . .	5,050,000	116	..	0.7				
P.M. . .	5,010,000	114	..	0.8				
A.M. . .	5,080,000	116	..	0.5				
P.M. . .	4,980,000	114	..	0.6				
A.M. . .	5,200,000	114	..	0.6				
A.M. . .	5,110,000	114	..	3.0				
P.M. . .	5,180,000	115	..	1.2				
A.M. . .	5,260,000	116	..	1.5				
P.M. . .	5,200,000	115	..	0.7				
A.M. . .	5,290,000	116	..	1.0				
P.M. . .	5,110,000	116	..	0.6				
A.M. . .	5,010,000	118	..	0.4				
	4,960,000(V)	..	119	..	46.5	9.3	54.30	7.63
P.M. . .	5,030,000	114	..	0.3				
A.M. . .	5,020,000	116						
P.M. . .	5,110,000	116	..	0.3				
A.M. . .	5,380,000	116	..	0.2				
P.M. . .	5,210,000	115	..	0.3				
A.M. . .	5,280,000	116	..	0.2				
A.M. . .	5,400,000	118	..	0.3				
A.M. . .	5,330,000	118	..	0.3				
A.M. . .	5,290,000(V)	..	118	..	45.9	8.6	49.80	7.67
	5,500,000	120	..	0.4				

V = Venous blood used.

An analysis of the red blood cell counts revealed them in similar fashion to have been moderately affected. The greatest increase occurring, as shown in Table I, did not exceed 700,000 from the average control value, while in Tables II and III the greatest increase was not in excess of 300,000 from the average of their respective control values.

TABLE II.

Time.	Red blood cells per c.mm.	Hemoglobin (cap.).	Hemoglobin (ven.).	Reticulocytes, per cent.	Hematocrit, per cent of cells.	Individual cell volume	Blood iron.	Mean diameter, microns.
A.M. . .	5,090,000(V)	..	114	..	40.6	7.9	42.02	7.69
	4,980,000	112	..	0.7				
A.M. . .	4,090,000	109	..	0.5				
A.M. . .	5,110,000	107	..	0.4				
		Liver extract started.						
A.M. . .	5,140,000	109	..	0.5				
P.M. . .	5,080,000	104	..	0.5				
A.M. . .	5,170,000	107	..	0.5				
P.M. . .	5,020,000	109	..	0.6				
A.M. . .	5,020,000	107	..	0.4				
P.M. . .	5,030,000	108	..	0.4				
A.M. . .	5,080,000	106	..	0.5				
A.M. . .	5,130,000	106	..	0.7				
P.M. . .	5,240,000	108	..	1.3				
A.M. . .	5,340,000	110	..	0.9				
P.M. . .	5,460,000	108	..	0.8				
A.M. . .	3,300,000	110	..	0.5				
P.M. . .	5,100,000	110	..	0.4				
A.M. . .	4,940,000	110	..	0.3				
	5,020,000(V)	..	117	..	47.3	9.4	45.30	8.05
P.M. . .	4,990,000	108	..	0.3				
A.M. . .	5,180,000	110	..	0.3				
A.M. . .	5,480,000	110	..	0.3				
P.M. . .	5,190,000	111	..	0.3				
A.M. . .	5,230,000	112	..	0.2				
A.M. . .	5,400,000	112	..	0.3				
A.M. . .	5,480,000	113	..	0.3				
	5,220,000(V)	..	112	..	45.9	8.8	46.80	7.63
	5,630,000	113	..	0.3				

V = Venous blood used.

In Table IV the onset of an acute upper respiratory infection in this subject on the eighth day forced him to discontinue the extract. However, up to that time the findings in his case were in accord with the others. The counts on the whole show a tendency toward a moderate but sustained red blood cell elevation during the latter

half of the experiment. There was, however, no evidence of an immediate or excessive rise to striking values in any case.

TABLE III.

Time.	Red blood cells per c.mm.	Hemoglobin (cap.).	Hemoglobin (ven.).	Reticulocytes, per cent.	Hematocrit, per cent of cells.	Individual cell volume	Blood iron.	Mean diameter, microns.
A.M.	5,000,000(V)	..	107	..	43.8	8.7	42.84	7.73
	5,010,000	109	..	0.5				
A.M.	5,140,000	108	..	0.7				
P.M.	5,080,000	109	..	0.5				
A.M.	5,110,000	110	..	0.4				
	Liver extract started.							
A.M.	5,060,000	111	..	0.3				
P.M.	5,030,000	120	..	0.5				
A.M.	5,200,000	107	..	0.6				
P.M.	5,070,000	116	..	0.5				
A.M.	5,180,000	117	..	0.4				
P.M.	5,050,000	109	..	0.4				
A.M.	5,200,000	114	..	0.5				
A.M.	5,180,000	110	..	1.1				
P.M.	5,320,000	109	..	1.4				
A.M.	5,540,000	112	..	1.0				
P.M.	5,380,000	111	0.8					
A.M.	5,340,000	110	..	0.6				
P.M.	5,020,000	112	..	0.4				
A.M.	5,040,000	110	..	0.4				
	4,980,000(V)	..	109	..	45.3	9.0	46.8	7.91
P.M.	5,090,000	111	..	0.3				
A.M.	5,100,000	112	..	0.3				
P.M.	5,190,000	112	..	0.3				
A.M.	5,510,000	112	..	0.3				
P.M.	5,210,000	110	..	0.2				
A.M.	5,260,000	112	..	0.3				
A.M.	5,320,000	114	..	0.3				
A.M.	5,340,000	114	..	0.4				
A.M.	4,990,000(V)	..	115	..	43.8	8.8	46.8	7.65
	5,390,000	114	..	0.3				

V = Venous blood used.

Hemoglobin values were not greatly altered, but point again toward a higher general average in the latter days of the test.

The blood-iron level was slightly increased in 3 subjects. The individual cell volumes showed a slight intermediate increase, due perhaps to the increased number of young cells, although the

diameters were irregularly affected, giving an intermediate rise in 2 cases with a later return to control sizes.

TABLE IV.

Time.	Red blood cells per c.mm.	Hemoglobin (cap.).	Hemoglobin (ven.).	Reticulocytes, per cent.	Hematocrit, per cent of cells.	Individual cell volume	Blood iron.	Mean diameter, microns.
A.M. . .	4,600,000(V)	..	98	..	39.5	8.4	40.50	7.61
A.M. . .	4,610,000	100	..	0.6				
A.M. . .	4,890,000	105	..	0.5				
A.M. . .	4,990,000	104	..	0.5				
A.M. . .	5,180,000	105	..	0.5				
	Liver extract started.							
A.M. . .	5,102,000	103	..	0.4				
P.M. . .	5,010,000	105	..	0.7				
A.M. . .	5,120,000	104	..	0.4				
P.M. . .	4,990,000	105	..	0.5				
A.M. . .	5,100,000	104	..	0.4				
P.M. . .	5,140,000	104	..	0.7				
A.M. . .	5,160,000	104	..	0.8				
A.M. . .	4,990,000	105	..	1.1				
P.M. . .	5,090,000	105	..	0.7				
A.M. . .	5,060,000	105	..	0.5				
P.M. . .	5,100,000	104	..	0.5				
A.M. . .	4,890,000(V)	..	102	..	41.0	8.5	41.50	7.96
	5,090,000	104						

V = Venous blood used.

The icteric index remained normal throughout.

The only subjective symptoms noted during the course of the experiment were a moderate nausea which followed almost immediately after taking a fairly large dose (3 or 4 vials) upon an empty stomach and a slight diarrhea lasting from four to six days. No headache, dizziness, epistaxis or acrocyanosis occurred. The subjects in general felt quite well.

These findings are very much in accord with certain other investigations. Minot, Murphy and Stetson,[5] using cooked liver, were able to demonstrate only trivial increase in either hemoglobin or red blood cells. Similarly, Neidhardt and Bannasch,[6] on diets of 500 gm. of raw liver for periods up to thirty days, obtained only slight increases in red blood cells and hemoglobin. Jungmann,[7] with a diet identical with that of Neidhardt and Bannasch, reported that the red blood cell counts were practically unchanged. Cornell[8]

found no change in the blood of 4 normal persons who ingested 240 gm. of raw liver pulp daily for four weeks.

From these observations one may conclude that blood formation in normal individuals may be enhanced by the ingestion of large amounts of liver or liver extract, but that a striking change does not occur.

Neidhardt and Bannasch believe that there is an increased hemolysis, as shown by the increase of urobilin in the urine; but on the one hand the urobilin determination in the urine is a very crude one, and a quantitative determination of urobilin in both stool and urine would be necessary to demonstrate an increased hemolysis. On the other hand, the icteric index in our cases was not increased, which indicates that no pathologic hemolysis took place. The urine tested for urobilin at the conclusion of our observations was negative.

As suggested by Minot and Murphy,[9] and later substantiated by the work of Castle,[10] it is very probable that liver contains an essential element which is necessary for the formation of normal and durable red blood cells. Only if this factor is absent, and the red blood cell count low, as in pernicious anemia, do we get the typical and striking liver effect.

Conclusions. 1. There was observed a slight rise in the reticulocytes, an increase in red blood cells and percentage of hemoglobin, together with a slight rise in the blood-iron level following the ingestion of the contents of 8 vials of liver extract daily.

2. Striking changes in the blood did not occur nor were the clinical symptoms or signs of polycythemia observed during such treatment.

3. There was no evidence to suggest increased hemolysis of the blood during the period of observation.

BIBLIOGRAPHY.

1. Watkins, C. H., Johnson, R., and Berglund, H.: The Effect of Liver Extract on Erythrocytes and Reticulocytes in Normal Individuals, Proc. Soc. Exp. Biol. and Med., 1928, **25**, 720, 835.

2. Murphy, W. P., and Fitzhugh, G.: Red Blood Cell Size in Anemia; Its Value in Differential Diagnosis, Arch. Int. Med. (in press).

3. Murphy, W. P., Lynch, R., and Howard, I.: The Value of Whole Blood Iron Determinations (in press).

4. Murphy, W. P.: Biliary System Function Tests, Arch. Int. Med., 1926, **37**, 797.

5. Minot, G. R., Murphy, W. P., and Stetson, R. P.: The Response of the Reticulocytes to Liver Therapy, Am. J. Med. Sci., 1928, **175**, 581.

6. Neidhardt, K., and Bannasch, K.: Effect of Liver Diet on Healthy Organism, Ztschr. f. klin. Med., 1929, **111**, 292.

7. Jungmann, P.: The Mechanism of Liver Treatment in Pernicious Anemia, Klin. Wchnschr., 1928, **7**, 441.

8. Cornell, B. S.: Effect of Liver in the Diet of Normal Persons, Canadian Med. Assn. J., 1928, **28**, 394.

9. Minot, G. R., and Murphy, W. P.: A Diet Rich in Liver in the Treatment of Pernicious Anemia, J. Am. Med. Assn., 1927, **89**, 759.

10. Castle, W. B.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia, Am. J. Med. Sci., 1929, **178**, 748, 764.

THE INFLUENCE OF GASTRIC JUICE ON ERYTHROPOIESIS IN PERNICIOUS ANEMIA.

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A comprehensive survey of the data suggesting a causal relationship between the gastrointestinal tract and pernicious anemia, in 1926, by Ivy,[1] constitutes an accurate résumé of the literature to that date. For the present purposes suffice it to say that for years laboratory and clinical evidence had been accumulating in support of this interrelation. On one point only had there developed an unanimity of opinion among workers in this field, namely, the constancy of achylia gastrica in patients with pernicious anemia. Levine and Ladd[2] in an analysis of 143 cases of pernicious anemia reported the astounding figure of 99 per cent in which achlorhydria was established. All of the further evidence in this matter was, as the above, purely inductive for a causal relationship between the two conditions, and it is beyond the scope of the present note to reiterate these details.

It remained for Castle[3,4,5,6] in a series of original and revealing studies to attack this problem by the direct method of experimentation. His observations may be listed as follows:

(*a*) The product of the normal gastric digestion of a beef meal, regurgitated and then further incubated *in vitro* with hydrochloric acid, when fed to patients with pernicious anemia, induced reticulocyte responses with remissions in the blood picture comparable to those from liver therapy.

(*b*) Beef alone is incapable of such action.

(*c*) Diluted hydrochloric acid will not induce such reactions.

(*d*) The product of the interaction between beef on one hand and commercial pepsin and hydrochloric acid on the other, *in vitro*, proved inert.

(*e*) Normal gastric juice and beef incubated together *in vitro* with hydrochloric acid and then administered to patients with pernicious anemia gave rise to characteristic remissions.

(*f*) Normal gastric juice incubated *in vitro* with an indifferent protein as casein developed no potency with reference to erythropoiesis.

(*g*) Normal gastric juice administered alone and at a sufficient interval after meals led to no regular erythropoietic response. Where

a slight response was noted, still further rises resulted when similar quantities of gastric juice and beef muscle were incubated together *in vitro* and then given to the same subjects.

Wilkinson[7] reported results rather contradictory to those of Castle on the administration of gastric juice to a patient with pernicious anemia. Exercising due precautions to obtain an active normal gastric juice with or without histamin, 150 to 200 cc. was given during meals. (It is not possible to determine from the report whether this amount represents the total dosage for a day or that given at each of three meals.) The single case cited in detail received 150 to 200 cc. of fresh gastric juice daily with the noonday meal. The initial level of erythrocytes was 3,850,000 and the hemoglobin 100 per cent. A control period of exhibition of hydrochloric acid and pepsin had led to a decline in the blood picture. On the administration of gastric juice a reticulocyte rise to 4 per cent was noted on the twenty-fourth day, when the erythrocytes numbered over 4,000,000. It will be noted that the initial level of erythrocytes (3,850,000) precluded a true reticulocyte response[8] regardless of the agent used. While the reticulocyte rise is appreciable considering this point, the author is not justified in attributing the subsequent fall of the reticulocytes to the institution of liver therapy. Reticulocyte responses in pernicious anemia to any form of therapy are not to be anticipated with erythrocyte counts exceeding 3,000,000.

In view of the possible question awakened by Wilkinson's report and the difficulties attendant upon clinical studies of this type the two following experiences are cited:

Case Reports. CASE I.—A white, single male, farmhand, aged forty-one years, was admitted to the Hospital on November 7, 1929, with a history of weakness, which began the previous January with an attack of so-called "flu," at which time he was delirious. Convalescence was marked by weakness and pallor, and in February he was told to take 1 vial of liver extract daily. This dosage was continued up to the time of admission, except for a period of three weeks in June. He consulted a physician in July when the weakness became more marked and was advised that liver therapy be continued and that iron be added. Weakness, however, continued unabated and in October, 1929, the patient was forced to go to bed, where he remained until admission to the hospital. His history also included recurrent soreness of the tongue, epistaxis, dyspnea, nocturia, and 27 pounds loss of weight since January, 1929. Past medical, social, and family histories were irrelevant.

The pertinent physical findings included a sallow, lemon-colored skin, oral sepsis, dental caries, atrophic tongue with visible papillæ, pale mucous membranes, venous hum at the base of the neck, systolic murmur over entire precordium, palpable liver edge, quadriceps and general muscular weakness, and decreased vibratory perception over the tibiæ.

Laboratory examination on admission showed an erythrocyte count of 1,050,000, with a hemoglobin of 20 per cent. Fractional aspiration of the gastric contents following subcutaneous histamin injection revealed the absence of free hydrochloric acid. The stools contained no ova, parasites nor motile organisms. The icterus index was 15.

A diagnosis of pernicious anemia with early cord involvement was made, and the failure of response to a potent liver extract was attributed to the inadequate dosage.

The day following admission 100 cc. of gastric juice was given with each meal. The average titration of this gastric juice showed a free acid content of 33 degrees. This procedure was continued for a period of six days without a reticulocyte response. The erythrocyte count at the conclusion of this period showed 630,000 cells, with less than 10 per cent hemoglobin. Because of the patient's precarious condition liver extract (Eli Lilly & Co. No. 343), 1 vial three times a day was begun; and in the absence of an adequate response in the blood picture at the end of a further period of six days, a blood transfusion was given. Following this procedure a further reticulocyte response was noted with a rise in the erythrocyte counts. Twelve days after the blood transfusion and after eighteen days of administration of liver extract (equivalent of from 300 to 500 gm. of liver daily) the erythrocyte count was 3,270,000, with 53 per cent hemoglobin. Hence the response of the blood picture to accepted therapy would be deemed satisfactory (Fig. 1).

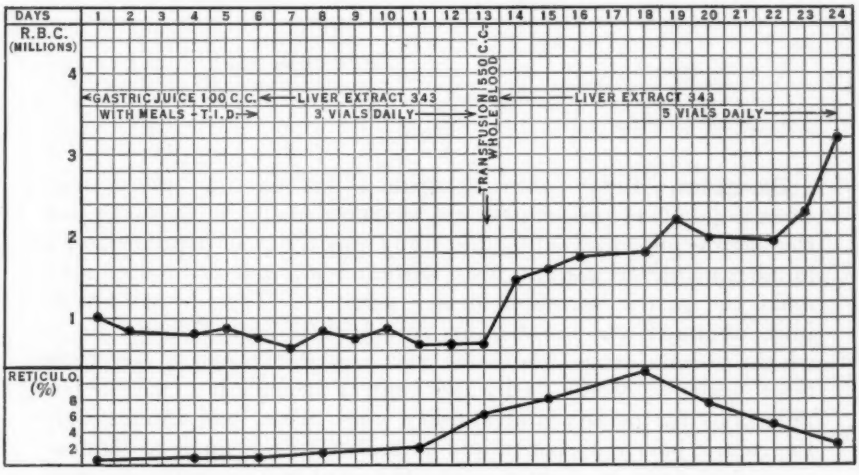

FIG. 1

CASE II.—A retired white farmer, aged seventy-three years, was readmitted to the Hospital on December 9, 1929, having been discharged on December 12, 1928 with a diagnosis of pernicious anemia after an excellent remission from liver therapy. Shortly after his discharge he had neglected to continue with the liver extract as advised; and on readmission physical examination again showed the lemon-yellow pallor, bald tongue, cardiac enlargement, papable liver and right kidney, thickening of the radial arteries, loss of vibratory sensation in the lower extremities, and general muscular weakness of his earlier hospital stay.

Laboratory examinations on admission included a blood count of 1,640,000 erythrocytes, with 35 per cent hemoglobin. The icterus index was 8.

A diagnosis of pernicious anemia with posterolateral degeneration of the cord was reaffirmed.

Beginning the day following admission, the patient was given 200 cc. of

gastric juice with each meal. The average titration showed a free acid content of 33 degrees. Nine days after this treatment was begun, the average reticulocyte count was somewhat above normal, but their number never exceeded 5.2 per cent of the total erythrocytes. At the end of eighteen days, the patient was discharged. His blood count then showed 1,550,000 red blood cells and 47 per cent hemoglobin (Fig. 2).

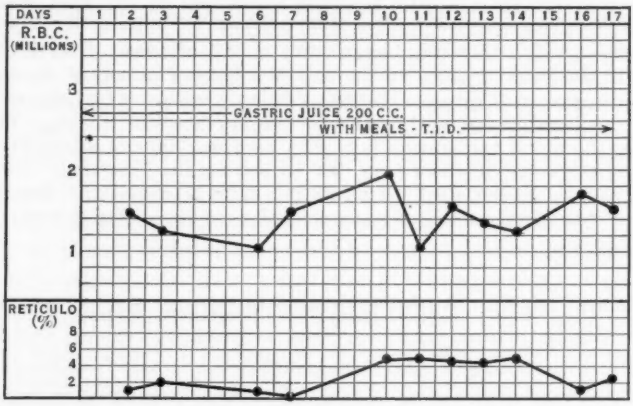

FIG. 2

Discussion. Before entering upon a discussion of these cases certain details of procedure must be considered. In the first place the gastric juice utilized in this study was the pooled product of a number of gastric aspirations. Histamin was not utilized to augment the gastric secretion in any instance. The normal gastric juice obtained was titrated for free acidity, and if found to be within normal range, the same was passed through a Berkefeld filter, sealed in sterile flasks and kept in an icebox. Daily determinations for acidity and sterility were made, and interestingly the gastric juice maintained its free acidity with little or no fluctuation for as long as six weeks. At the same time sterility was preserved. This observation, of course, placed the responsibility for the usual loss of free acidity when a gastric content is allowed to stand upon bacterial or fungous growth and proteids, such as mucin, which may be removed by the Berkefeld filter.

In analyzing the results of the administration of normal gastric juice to these 2 patients, one notable difference presents itself, namely, a low-grade response of the reticulocytes in Case II as compared with an absence of response in Case I. In neither instance did a significant numerical rise of the erythrocytes occur. It may be argued that Case I did not receive the gastric juice in sufficient quantity (one-half the daily amount received by Case II) nor long enough to manifest a hematopoietic effect, whereas Case II obviously had an adequate trial. This argument cannot be controverted. In view of Castle's observations,[6] what would seem a more logical

explanation of the difference resides in the fact that while both received the same diet, Case II ate his meat regularly and Case I was unable to partake of the same. As Castle[6] has pointed out, the interaction between ingested beef and normal gastric juice administered close to the former may readily occur in the stomach of a pernicious anemia patient with a resultant product which is responsible for the blood remissions in pernicious anemia.

Conclusion. In conclusion it may be stated that these studies, meager though they be, support Castle's contention that normal gastric juice alone does not contain the active maturating factor essential to erythropoiesis.

REFERENCES.

1. Ivy, A. C.: The Relation of the Gastrointestinal Tract to Pernicious Anemia, Northwest Med., 1926, **25**, 399.

2. Levine, S. A., and Ladd, W. S.: Pernicious Anemia: A Clinical Study of 150 Consecutive Cases with Special Reference to Gastric Anacidity, Bull. Johns Hopkins Hosp., 1921, **32**, 254.

3. Castle, W. B., and Locke, E. A.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia, J. Clin. Invest., 1929, **6**, 2.

4. Castle, W. B.: The Etiologic Relationship of Achylia Gastrica to Pernicious Anemia, Proc. Roy. Soc. Med., 1929, **22**, 58.

5. Castle, W. B.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia. I. The Effect of the Administration to Patients With Pernicious Anemia of the Contents of the Human Stomach Recovered After the Ingestion of Beef Muscle, Am. J. Med. Sci., 1929, **178**, 748.

6. Castle, W. B., and Townsend, W. C.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia. II. The Effect of the Administration to Patients with Pernicious Anemia of Beef Muscle After Incubation with Normal Human Gastric Juice, Am. J. Med. Sci., 1929, **178**, 764.

7. Wilkinson, J. F.: Pernicious Anemia—Preliminary Report on the Results Obtained by Treatment with Certain Preparations of Stomach, British Med. J., 1930, i, 236.

8. Minot, G. R., Murphy, W. P., and Stetson, R. P.: Response of the Reticulocytes to Liver Therapy, Particularly in Pernicious Anemia, Am. J. Med. Sci., 1928, **175**, 581.

INCIDENCE OF THE SICKLE-CELL TRAIT IN INDUSTRIAL WORKERS.

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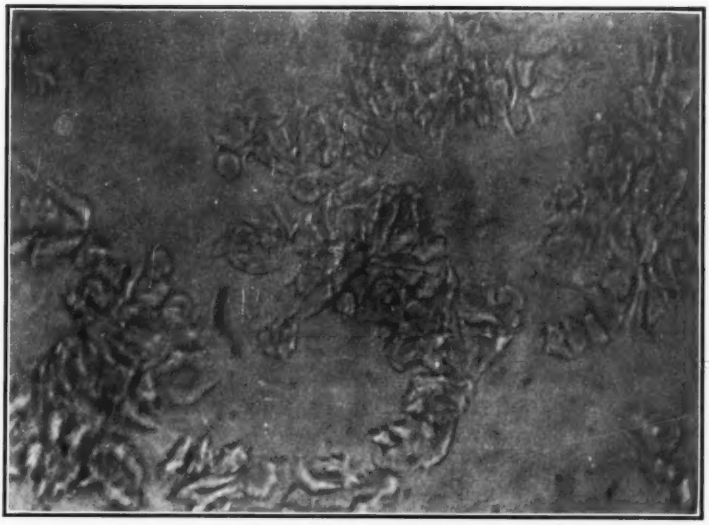
The attention of the profession has been drawn repeatedly during the past two decades to the occurrence of a new or newly-discovered nosologic entity which, on account of a numerical decrease of the red blood corpuscles, associated with a peculiar crescentic conformation of a varying percentage of these cells, has been designated sickle-cell anemia. The occurrence of such cells was first noted in 1889 by the French hematologist, Hayem,[1] and in 1910 Herrick,[2] of Chicago, reported a case of sickle-cell anemia, thus giving an impetus to the study of the disease in this country.

The most characteristic signs and symptoms of this disease appear to be a yellow or greenish-yellow discoloration of the scleræ, presence or history of leg ulcer, abdominal crises, lymph glandular enlargement, muscle and joint pains, sickle cells varying from 1 to 95 per cent of the total number of red blood corpuscles, anemia and urobilinuria. During the acute phases of the disease there is moderate pyrexia. The spleen may or may not be enlarged. The condition occurs almost exclusively in the negro race, although 1 case has been reported in an Arab boy, who possibly had some admixture of negro blood,[3] and 4 white cases[4,5] have been described in which there was no evidence to sustain any suspicion of an Ethiopian taint. It is marked by remissions and exacerbations, the remissions being largely devoid of subjective symptoms, and accompanied by improvement in the objective signs, as well as a corresponding change in the laboratory findings. Aside from the disease itself, and in a large majority of cases occurring without active signs of ill health, the phenomenon of drepanocytosis is observed in the sickle-cell state, trait or aptitude or latent sickle-cell anemia, as it is variously called. The term latent sickle-cell anemia should not, however, be used as a synonym of sickle-cell trait, but if employed at all, should be reserved to designate those periods of remission in drepanocytic anemia when the disease is practically quiescent. It seems to be established that the anemia occurs more frequently in those with the sickle-cell trait than in those whose blood is normal in this respect; in other words, that the trait is a predisposing factor in the development of the anemia.[9] Some authors even regard the trait as a very mild form of the disease, of which the active anemia is a severer manifestation,[6] although the former has been found to be entirely compatible with good health and with long life, while the latter is not considered conducive to either. The trait has been observed to remain in some cases after the anemia and its accompanying symptoms have cleared up[4] (remissions) and even after splenectomy[3,9,10] (presumptive cure). The distorted cells or poikilocytes found in these conditions are designated drepanocytes, from the Greek word, δρεπάνος, meaning sickle, and the name is thus descriptive of the morphology. They have also been called meniscocytes in reference to their crescentic shape. The drepanocytic status has been reported from different cities as occurring in from 5[11] to 7[9] or 7.5[12] per cent of the negroes examined. These figures represent the incidence in hospital or dispensary patients who presumably were present because of disease or injury. In order to determine the incidence among the negro male population in this locality it was decided that 100 negro applicants for employment should be examined, though to date nearly twice that number have been subjected to study. Interest was felt also in the question of the ratio of the occurrence of the sickle-cell trait in patients applying for treatment to that in healthy workers applying for remunerative occupation. The investigation was under-



Sickle cells in moist preparation. Variations in shape in the distorted forms are evident. In the smaller cells the refractive index appears to be increased.

taken primarily to ascertain whether or not the sickle-cell trait is to be regarded as a definite industrial hazard. The examination in each instance consisted of three parts:

1. A brief history inquiring into past illnesses, with special reference to the occurrence of joint and muscle pains, abdominal crises and ulcers.

2. A general physical examination, giving particular attention to scleral color anomalies, lymph-node enlargement and hypertrophied tonsils, ulcers, especially ulcus cruris or resultant scars, and condition of the abdomen.

3. Study of moist blood films made by placing a drop of fresh blood on a slide, covering it with a coverslip and sealing with vaseline to prevent drying. These preparations were then observed daily for six days or longer.

As the individuals examined were all applying for work, some of them were no doubt unduly reticent in relating their previous untoward symptoms, and to that extent the histories must be discounted. The number who had "never been sick a day in their lives" was almost unbelievably large. Nevertheless, with the use of patience and diplomacy, it is believed fairly accurate data were secured. Yet in only 1 of those with positive blood findings did the history disclose any symptoms in the past which might possibly have been interpreted as representing the acute phase of the disorder or active drepanocytic anemia. In this case there was a history of an acute attack of "rheumatism" at twenty-two years of age (the present age being forty-two years) and of attacks of "indigestion" following dietary indiscretions, these attacks being of infrequent occurrence and distributed over a long period of time. In those with negative blood findings there was a history of joint pains in 3, of indigestion or abdominal cramping in 15 and of leg ulcers in 2. The small number of positives used in the comparison, and the manifold interpretations which might be accorded the symptoms mentioned, would rob these figures of any significance except to indicate that the history is of but little value in detecting individuals possessed of the sickle-cell trait. Certain symptoms as related in the anamnesia might, however, be regarded as suggestive of the condition, although a negative history would not necessarily nullify a presumption of its presence. As the sickle-cell trait has been demonstrated in patients who have had sickle-cell anemia,[4] a clear history of this disease would at least be suggestive of the presence of the trait.

The physical examinations not only did not reveal any pathognomonic sign associated with the sickle-cell condition, but also failed to demonstrate any probable sign or syndrome on which a diagnosis might reasonably be hazarded. In only 5 of the 100 subjects were the scleræ and episcleræ clear and devoid of some color changes, although none of these 5 were in the positive group. The predominating color was a brownish hue, sometimes with flecks of a darker

brown tint; occasional variations were yellowish-brown, cream colored or even reddish-brown. Quite a few (16) showed a light slaty-blue tint of the scleræ, with perhaps 2 or 3 dark-blue pin-head-sized macules on this background. However, none of these latter were found to have sickle cells, nor was there any indication that these blue sclerotics were of the type associated with fragility of the bones.

The inguinal lymph nodes were palpable in 95 per cent of the men examined and in all of the positive cases. General lymphadenopathy was noted in 2 of the positive and in 30 of the negative cases, thus maintaining practically the same proportion. In none of the positive cases was the spleen demonstrably enlarged. Leg ulcers were not present in any of the men examined. The age, weight, blood pressure, muscular tone and development, presence of focal infections and bluish mottling of gums and palate were likewise considered and found to be apparently without bearing or influence on the condition. It occurred both in the pure black and in those of mixed blood. The typical greenish-yellow scleræ of the active anemia is dependent on erythrocyte destruction and, as was to be expected, was not observed with the sickle-cell state. The same remarks are applicable to the urobilinuria, Erlich's aldehyde test showing absence of that condition in the positive cases reëxamined. Urobilinuria, however, has been reported in the sickle-cell trait, apparently in the absence of active hemolysis.

In examining the slides for sickle cells it was observed that the red corpuscles assumed the typical shapes after varying lengths of time, the phenomenon occurring sometimes on the first day and sometimes as late as the fifth day. The change is probably brought about in susceptible cells by the consumption of oxygen and the formation of carbon dioxid resulting from cell metabolism.[9] Other factors are not without influence.[9,4] Being unfamiliar with the study of moist preparations, some confusion was at first occasioned by the occurrence of poikilocytes not of the typical sickle-cell shapes. In these slides the red blood cells appeared smoothly outlined and distorted into various shapes, such as cup-shaped, club-shaped, horseshoe-shaped, sinuous forms, falcate, scaphoid and others. This change was found usually in drying films, and it is thought was due to osmosis through the cell membrane, though not all drying films showed this change. Reëxamination of the men in this group gave negative results, and similar forms were noted in a control series in Mexicans; hence, the slides were not regarded as positive. Some difficulty was experienced in attempting to check the true positives, as due to rapid labor turnover only 5 of 10 positive subjects could be located for reëxamination. Of these 5, 3 remained positive and 2 which were positive on first examination were negative at a later date. Thus it appears that in a given case examination may be positive for the sickle-cell trait at one time, at another time negative and that, therefore, in a group the apparent

incidence of susceptibility may be less than the real incidence, as some possessed of the trait may at the time of examination render a negative film. Some writers assert that in persons showing this phenomenon it is a constant finding, but the results of our check-up show that this is not uniformly the case. Anderson[13] mentions an instance in which a patient showed no progressive sickling while in the hospital, but two weeks after his discharge showed from 90 to 95 per cent sickling in moist preparations twenty-four hours old.

Wassermann tests were not obtained except in 1 case, in which it proved to be negative. Hemoglobin estimation by the Tallqvist scale varied, but the lowest readings were 75 to 80 per cent. In 150 men, 10, or 6.63 per cent, of sickle-cell trait were found, which is in close agreement with the percentage reported from other localities. This indicates a similar incidence in healthy industrial workers and in hospital or dispensary patients, although it must be remembered that the personnel of this group did not include any women.

Conclusions. 1. The history, however important in other respects, is of little value in the detection of subjects with sickle-cell trait, but may be suggestive.

2. The physical signs are not diagnostic. Absence of scleral color anomalies or of lymph-node enlargement may possibly be regarded as evidence against the presence of the sickle-cell trait in any one individual.

3. Examination of moist blood films is a simple method of diagnosing the condition.

4. The percentage of the occurrence of the sickle-cell trait in 150 negro men applying for work was 6.67 per cent.

The accompany microphotograph was made by Dr. E. F. Cooke.

BIBLIOGRAPHY.

1. Hayem: Quoted in Editorial: Sickle-shaped Red Blood Cells, J. Am. Med. Assn., 1929, **92**, 2105.

2. Herrick, J. B.: Peculiar Elongated and Sickle-shaped Red Blood Cells in a Case of Severe Anemia, Arch. Int. Med., 1910, **6**, 517.

3. Archibald, R. G.: Trans. Roy. Soc. Trop. Med. and Hyg., 1926, **19**, 389.

4. Sydenstricker, V. P.: Med. Clin. North America, 1929, **12**, 1451.

5. Cooley, T. B., and Lee, P.: Sickle-cell Anemia in a Greek Family, Am. J. Dis. Child., 1929, **38**, 103.

6. Alden, H. S.: Sickle-cell Anemia: Report of Two Cases from Ohio Illustrating Its Hemolytic Nature, Am. J. Med. Sci., 1927, **173**, 168.

7. Browne, E. Z.: Sickle-cell Anemia, Med. Clin. N. Am., 1926, **9**, 1191–97.

8. Stewart, W. B.: Sickle-cell Anemia: Report of a Case With Splenectomy, Am. J. Dis. Child., 1927, **34**, 72.

9. Hahn, E. V.: Sickle-cell (Drepanocytic) Anemia, Am. J. Med. Sci., 1928, **175**, 206.

10. Bell, A. S., *et al.*: Sickle-cell Anemia: Two Cases with Splenectomy, Am. J. Dis. Child., 1927, **34**, 1923.

11. Smith, J. H., Jr.: Sickle-cell Anemia, Med. Clin. North America, March, 1928, vol. **11**.

12. Cooley, T. B., and Lee, P.: The Sickle-cell Phenomenon, Am. J. Dis. Child., 1926, **32**, 334.

13. Anderson, H. B.: Sickle-cell Anemia, Am. J. Med. Sci., 1926, **171**, 641.

CHLOROTIC ANEMIA OF PREGNANCY.

A Report of Three Cases.

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Since the first American description of an anemia of pregnancy by Walter Channing,[1] in 1842, there have been many case reports of this condition with a variety of causative factors.

Alder,[2] in 1924, classified the anemias associated with pregnancy as follows: I. Anemia with pregnancy: (*a*) chlorosis; (*b*) post-hemorrhagic anemia; (*c*) congenital hemolytic icterus; (*d*) previously present primary pernicious anemia; (*e*) leukemia, acute or chronic; myelocytic or lymphocytic. II. Anemia from pregnancy: (*a*) physiologic; (*b*) pernicious type of anemia of pregnancy.

Larrabee,[3] in 1925, divided his cases of anemia of pregnancy into a primary "pernicious" type and a secondary type.

O. H. P. Pepper,[4] in 1929, called attention to the fact that most of the publications on the subject of pregnancy anemia antedated modern hematologic and investigative methods.

Recently, 3 cases of the "pernicious" type of anemia of pregnancy were reported in detail by Peterson, Field and Morgan.[5] These cases all showed a "pernicious" type blood picture, but with free hydrochloric acid present in the gastric juice, and all recovered with liver therapy in exactly comparable manner to cases of Addisonian pernicious anemia not associated with pregnancy.

In striking contradistinction to these, the following 3 cases of "chlorotic" anemia of pregnancy all show a chlorosis-type blood picture with a complete and persistent achylia gastrica, and all show a quantitative response to iron therapy. In each of these the anemia definitely dated to the pregnancy and showed no tendency to recur afterward, but was otherwise exactly comparable to the chronic chlorosis described by Faber.[6]

Case Reports. Case I.—M. L., Boston City Hospital, No. 599357: A married, white housewife, aged thirty-four years, was admitted on December 19, 1929, complaining of weakness. The family history was entirely negative. During childhood, the patient had had chicken-pox, measles, mumps and pertussis. At the age of ten, she had had chorea. At fourteen, she had had quinsy sore throat, and had had frequent attacks of tonsillitis well into adult life. For many years, she had had headaches, chiefly frontal, usually occurring in the late afternoon. She had been delivered of eight normal children, an anencephalic monster, and had had three miscarriages at from three to seven months. During the last six years she had had some shortness of breath on exertion, palpitation, occasional dizziness, and was quickly exhausted after slight exertion. At puberty she had had a nervous

breakdown of an unknown type. On December 4, 1929, she was admitted to the Boston Lying-in Hospital and on December 8 was delivered of a nonviable anencephalic monster. Delivery was complicated by a compound presentation and hydramnios, but there was no abnormal bleeding. On the following day she became wildly delirious and was transferred to the Boston Psychopathic Hospital where she remained until admission to the Boston City Hospital. A pale yellow color of the skin and a moderate anemia were noted upon the patient's admission to the Psychopathic Hospital. The mental condition cleared rapidly and in ten days the patient was well enough to be transferred from the institution.

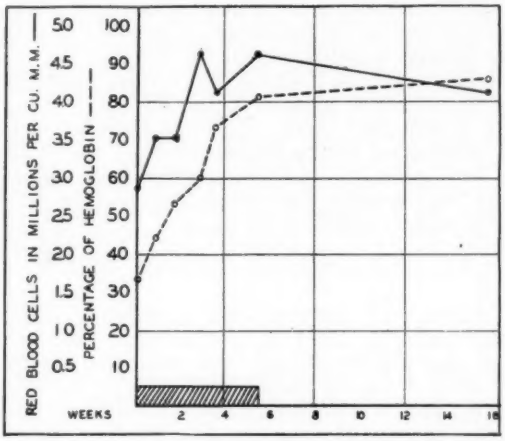

CHART I.—Case I. M. L. Cross-hatched area represents 6 gm. of iron and ammonium citrate daily.

On admission to the Boston City Hospital, it was noted that the patient was very pale and somewhat orthopneic. Oral sepsis and dental caries were present. The tongue was smooth and showed evidence of papillary atrophy about the margins. The heart was enlarged, the apex beat was in the fifth interspace, 10.5 cm. from the midsternal line. There was a middiastolic thrill at the apex and a loud systolic and short crescendo presystolic murmur at the apex. The systolic murmur was heard all over the precordium and was transmitted to the axilla. The second pulmonic sound was accentuated. The abdomen was lax; the uterus not felt. The reflexes, skin sensation, vibratory and position sense were all normal. The urine was of normal specific gravity, no albumin, no sugar; leukocytes and epithelial cells in the sediment. Stool was formed, brown; occult blood negative. Teleroentgenogram showed an enlarged heart. Electrocardiogram showed no abnormalities. Gastric analysis showed no free hydrochloric acid in the fasting contents or after an alcohol test meal, or after the subcutaneous injection of 0.5 mg. of histamin. The hemoglobin was 33 per cent (Sahli), red blood cells, 2,870,000; leukocytes, 8000. Stained smear showed abundant platelets, marked achromia, very slight anisocytosis and poikilocytosis. No abnormal white cells were seen. During the month in the hospital, the leukocytes varied from 6550 to 9500. The hemoglobin rose steadily until discharge, when it was 73 per cent and the erythrocytes were 4,100,000 (Chart I).

The only therapy administered was iron and ammonium citrate, 6 gm. daily. The diagnosis upon discharge was rheumatic heart disease, mitral stenosis and insufficiency, dental caries and chlorotic anemia of pregnancy.

Two weeks later the patient was seen, at which time the hemoglobin was 81 per cent, and red blood cells, 4,600,000. She was advised to discontinue further iron therapy. On April 11, 1930, she was again seen, at which time the hemoglobin was 86 per cent; red blood cells, 4,150,000; white blood cells, 7500. There was no achromia, anisocytosis or poikilocytosis seen in the stained smear. Gastric analysis at this time showed no free hydrochloric acid in the fasting contents, after an alcohol test meal or after 0.75 mg. of histamin subcutaneously. Pepsin and rennin content of the gastric juice were very low.

Case II.—M. L., Boston City Hospital, No. 599380: A married, white housewife, aged twenty-five years, was transferred on December 20, 1929, from the obstetric service for treatment of anemia. The family and past histories were entirely negative except for the fact that the patient had considered herself "run down" after a twin pregnancy one and a half years before. Two weeks before transfer to the medical service, she had been delivered of a normal male child. This had been her second pregnancy. She had had no bleeding during it nor was there any evidence of dietary insufficiency, but during the last two months of the pregnancy she had noted that she was becoming increasingly pale and, occasionally, had had a sensation of pins and needles in her fingers.

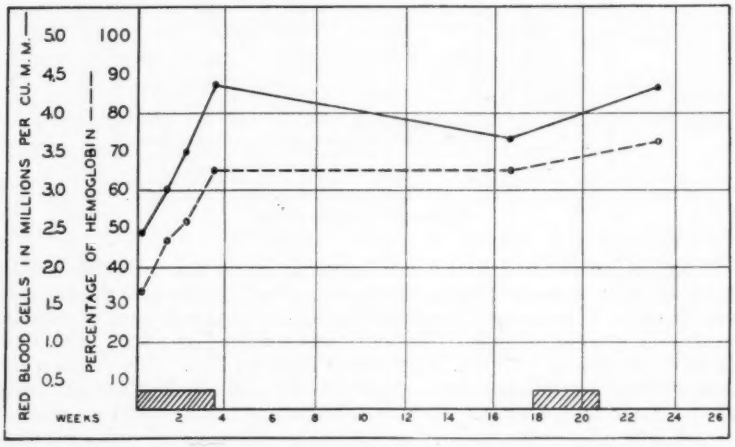

Chart II.—Case II. M. L. Cross-hatched area represents 6 gm. of iron and ammonium citrate daily.

Examination showed marked pallor of the skin and mucous membranes, a smooth tongue with evident marked papillary atrophy, and dental caries. The heart was enlarged to percussion with the apex 12 cm. to the left of the midsternal line, almost in the anterior axillary line. The first sound at the apex was blurred and was followed by a loud, rough systolic murmur. The second pulmonic was slightly accentuated. The abdomen was normal; the uterus not felt. The breasts were firm; the patient had not been permitted to nurse her baby. The reflexes, skin sensation, vibratory and position sense were entirely normal. The urine was of normal specific gravity with occasional traces of albumin on five of nine examinations, and occasional white cells in the sediment. The teleroentgenogram showed a heart enlarged transversely to the left. Electrocardiogram showed no abnormalities. Gastric analysis showed no free hydrochloric acid in the fasting contents, one hour after an alcohol test meal, or one-half hour after sub-

cutaneous injection of 0.5 mg. of histamin. The hemoglobin was 33 per cent (Sahli), erythrocytes, 2,450,000; leukocytes, 12,550. Stained smear showed increased platelets, marked achromia, very slight anisocytosis and poikilocytosis. No abnormal white cells were seen. During the stay in the hospital, the leukocytes varied from 6900 to 10,850. The hemoglobin rose steadily until discharge, three and a half weeks after admission, when it was 65 per cent and the erythrocytes were 4,380,000 (Chart II).

The only therapy administered was iron and ammonium citrate, 6 gm. daily. The diagnosis upon discharge was chlorotic anemia of pregnancy, and dental caries.

Three months later, on April 11, 1930, patient was again seen, at which time the hemoglobin was 64 per cent; erythrocytes, 3,650,000; leukocytes, 7300. Platelets appeared normal on smear. There was no achromia, anisocytosis or poikilocytosis. The gastric analysis at this time failed to show the presence of free hydrochloric acid in the fasting contents, after an alcohol test meal or after 0.75 mg. of histamin subcutaneously. Pepsin content was one-third the usual normal. Rennin content was very low. The patient stated that contrary to instructions she had not taken any iron after discharge. Six weeks later, on May 28, 1930, patient reported that she had taken iron and ammonium citrate, 6 gm. daily, for three weeks. The hemoglobin was 72 per cent; erythrocytes, 4,310,000; leukocytes, 8500. Stained smear showed very slight anisocytosis, otherwise it was normal.

Case III.—M. McK., Boston City Hospital, No. 594840: A married, white housewife, aged twenty-four years, was admitted during the last month of her second pregnancy from the Pre-natal Clinic, because of her anemia. The family history was entirely negative. The past history included measles and pertussis in childhood, and cervical adenitis from the age of twelve years on. Three years before admission biopsy had been done which revealed tuberculosis. Under light therapy the glands had markedly subsided. Seven years before admission she had had a twin pregnancy in which she suffered from mild eclampsia. However, both children were living and well. During the present pregnancy she had noted an increasing pallor of the skin and there had been occasional slight edema of the ankles, palpitation and dyspnea. Appetite had been good. There was no evidence of dietary insufficiency.

Physical examination showed marked pallor of the skin and mucous membranes and dental caries. The tongue appeared normal. There were several matted firm glands in the left superior cervical chain and a linear scar of biopsy. The heart was of normal size to percussion. The first sound was somewhat roughened at the apex and followed by a soft systolic murmur. The second pulmonic sound was somewhat accentuated. The uterus was palpated just below the xiphoid. Fetal movements were active. The reflexes, skin sensation, vibratory and position sense were entirely normal. The urine was of normal specific gravity. There was no albumin or sugar present. Epithelial and white blood cells were seen in the sediment. Stools were formed, brown; negative for occult blood. Teleroentgenogram showed a normal sized heart. Gastric analysis on two examinations showed no free hydrochloric acid after an alcohol test meal, or one-half hour after the subcutaneous injection of 0.5 mg. of histamin. The hemoglobin was 35 per cent (Sahli), the erythrocytes, 3,530,000; leukocytes, 9550. The stained smear showed slightly diminished platelets and marked achromia. No abnormal white blood cells were seen. During the six and a half weeks in the hospital, the leukocytes varied from 7750 to 11,000. On the day of delivery, November 15, 1929, five weeks after admission, the hemoglobin had risen to 68 per cent; erythrocytes, 4,750,000. Eleven days after delivery, the hemoglobin had further risen to 78 per cent; erythrocytes, 4,810,000 (Chart III).

The only therapy administered from the day of admission until discharge after delivery was 6 gm. of iron and ammonium citrate daily. The diagnosis upon discharge was chlorotic anemia of pregnancy, tuberculous cervical adenitis, and dental caries.

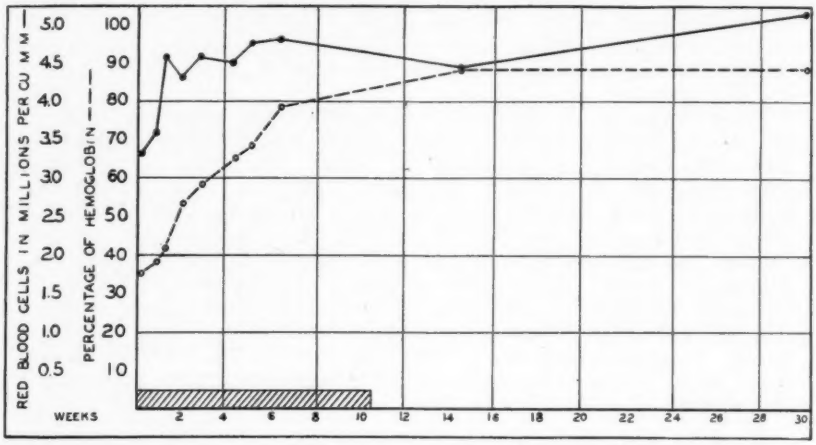

CHART III.—Case III. M. McK. Delivered at end of fifth week. Cross-hatched area represents 6 gm. of iron and ammonium citrate daily.

Two months later the patient stated that she had continued to take 6 gm. of iron and ammonium citrate daily for the first month after discharge. The hemoglobin was 88 per cent; erythrocytes, 4,410,000. The patient felt and appeared perfectly well. Four months subsequent to this visit, the patient was again seen at which time the hemoglobin was 88 per cent; erythrocytes, 5,210,000; leukocytes, 6720. The platelets on smear were normal in size and number; the white blood cells were normal; the red blood cells showed no achromia, no anisocytosis and no poikilocytosis. Gastric analysis at this time failed to show the presence of free hydrochloric acid in the fasting contents, after an alcohol test meal or after 0.75 mg. of histamin subcutaneously. Rennin and pepsin content of the gastric juice were very low. Lipase was completely absent.

Discussion. There are certain outstanding features in these 3 cases. All had a total achylia gastrica, including posthistamin specimens. This achylia is of very much less common occurrence than that after the usual test meals, which is itself rare enough in this age group. With the usual test meal, Smith[7] found 1 of his 8 cases of pregnancy anemia to have an achlorhydria, Hoskin and Ceiriog-Cadle reported 1,[8] Pepper 1,[4] and Larrabee 1,[3] but few such analyses have been made.

The blood picture in these 3 cases was typically that of chlorosis and, except for the fact that the anemia occurred with pregnancy, these cases are in every way comparable to the chronic chlorosis of Faber.[6] The work of Mettier and Minot[9] has suggested that this type of anemia is due to a conditioned iron deficiency in which

the achlorhydria presumably prevents the absorption of adequate amounts of iron from an ordinary diet, since they have shown that iron given therapeutically in an acid medium is more effective than when administered in a neutral or alkaline medium.

It is felt that in these 3 cases the diet furnished an adequate amount of iron, in spite of the possible faulty assimilation due to the achlorhydria, as long as there were no added demands upon the patients. Pregnancy, however, was just such an added burden, and until more iron was therapeutically added to the diet, anemia developed. As soon as iron was administered, hemoglobin was rapidly produced, stopping again when the administration of iron ceased, and, in Case II, again occurring when iron was ingested. Shulten[10] and Larrabee[3] have recently called attention to the value of iron in conditions of chlorosis and the work of Mettier and Minot has gone far in elucidating the mechanism of this deficiency.

In these 3 cases, the anemia definitely dated to the pregnancy, justifying the diagnosis of chlorotic anemia of pregnancy. It is believed, however, that any other added burden might well produce a similar anemia in patients with this anomaly of secretion, conditioning an iron deficiency.

Conclusions. 1. Three cases of chlorotic anemia of pregnancy are presented.

2. All 3 cases had a total achylia gastrica.

3. All 3 cases recovered on iron therapy alone.

4. It is believed that the added demands of pregnancy for hemoglobin resulted in an iron deficiency conditioned by the gastric achylia.

NOTE.—I wish to thank Dr. Ralph C. Larrabee for permitting me to publish the above cases.

REFERENCES.

1. Channing, W.: Notes on Anhaemia, Principally in Its Connections With the Puerperal State and With Functional Disease of the Uterus, With Cases, New England Quart. J. Med. and Surg., 1842, **1**, 157.

2. Alder, A.: Beitrag zur Kenntnis der Anämien in der Schwangerschaft, Ztschr. f. Geburtsh. u. Gynäk., 1924, **87**, 505.

3. Larrabee, R. C.: The Severe Anemias of Pregnancy and the Puerperium, AM. J. MED. SCI., 1925, **170**, 371.

4. Pepper, O. H. P.: A Review of Our Knowledge of the Anemias of Pregnancy, M ed. Clin. North America, 1929, **12**, 925.

5. Peterson, R., Field, H., and Morgan, H. S.: Liver Treatment in the Pernicious Anemia of Pregnancy, J. Am. Med. Assn., 1930, **94**, 839.

6. Faber, K.: Achylia Gastrica mit Anämie, Med. Klin., 1909, **5**, 1310; Anämische Zustände bei der Chronischen Achylia Gastrica, Berl. klin. Wchnschr., 1913, **1**, 958.

7. Smith, C. T.: An Anemia of the Puerperium, Surg., Gynec. and Obst., 1925, **40**, 223.

8. Hoskin, T. J., and Ceiriog-Cadle, E.: A Case of Severe Anemia of Pregnancy Simulating Addison's Anemia, Lancet, 1927, **1**, 433.

9. Mettier, S. R., and Minot, G. R.: The Effect of Iron on Blood Formation as Influenced by Changing the Acidity of the Gastric Contents in Certain Cases of Anemia, J. Clin. Invest., 1929, **7**, 510.

10. Shulten, H.: Zur Behandlung hypochromer Anämien mit maximalen Eisendosen, München. med. Wchnschr., 1930, **77**, 355.

EPITUBERCULOSIS.

A Study of Ten Cases for a Period of Over Two Years.

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Until recent years, pulmonary tuberculosis in children was regarded as extremely serious or almost uniformly fatal. Until 1920, children under three years of age who, on physical and roentgenologic examination revealed massive areas of pulmonary disease were, in the presence of a positive tuberculin reaction, invariably given a poor prognosis.

Eliasberg and Neuland[1] were the first to demonstrate that this conception was erroneous. In 1920, these authors reported a series of tuberculous children with massive involvement as described. The children studied by them became, after a period of time, entirely free from physical or roentgenologic pulmonary findings. Originally they had all manifested a well-defined clinical disease syndrome and had shown physical findings with dullness involving usually one whole lobe of a lung, most frequently an upper lobe, associated with bronchial breathing and few or no râles.

The onset in the cases studied was subacute; there was little or no fever and the general physical condition of the patients was good. The cough was not prominent. The extensive pulmonary physical findings were, in every instance, altogether out of proportion to the mild aspect of the clinical picture. The massive dullness over a whole lobe of the lung, usually an upper lobe, associated with bronchial breathing, seemed, to the writers, rather extraordinary in view of the mild fever, slight cough and general benign appearance of the patient.

The roentgenologic examination revealed a heavy, homogeneous density over the whole or greater part of the affected lobe; the density was usually sharply demarcated from the rest of the lung. These roentgenologic findings remained constant, usually for weeks or even for months without abrupt change. Then, after varying periods, the physical findings—dullness and bronchial breathing—gradually disappeared, and the Roentgen ray showed a gradual diminution in the density of the affected lobe. Finally, all physical and roentgenologic evidence, with the exception of enlarged hilus glands and the positive tuberculin reaction disappeared. It is

important to note that throughout the course of the condition, the sputum examination was always negative for tubercle bacilli.

Eliasberg and Neuland differentiated this infection from both caseous tuberculous pneumonias and from chronic, nontuberculous pneumonias. The gelatinous, caseous, tuberculous pneumonia (Virchow's "glatte pneumonie") is differentiated by the acute onset, high fever and usually rapidly fatal end. The chronic, nontuberculous pneumonias were differentiated by the history, usually present, of an acute pneumonic onset or by the preliminary history of measles, influenza or other respiratory infection. In addition, the course of the chronic, nontuberculous pneumonias is attended by more severe constitutional disturbances and, usually, by physical findings of lower lobe involvement associated with many râles or evidence of fibrosis.

One of the cases reported by Eliasberg and Neuland, an eleven-month-old infant, who had previously shown a fairly typical massive involvement of the right upper lobe, died of an intercurrent bronchopneumonia and empyema. The autopsy showed no tuberculous change in the right upper lobe. Unfortunately, the pathologic report is incomplete and does not deal with the matter of the hilus gland.

According to Eliasberg and Neuland[2] the nature of these massive pulmonary involvements was a nonspecific infiltration on a specific tuberculous soil and they called the condition epituberculous infiltration.

Although Eliasberg and Neuland were the first ones to bring out the characteristic clinical and roentgenologic pictures of this lung affection, the French medical literature called attention to this type of lung involvement as early as 1883, when Grancher[3] presented a similar clinical case and called it "splenopneumonia." Grancher considered his case as one of a subacute form of a bronchopneumonia. Bourdel[4] in 1886, in his book, "De la Splenopneumonie," summarized the known facts regarding Grancher's splenopneumonia by characterizing it as a peculiar form of a subacute bronchopneumonia, similar microscopically to hypostatic congestion but differing from it in that it contained a sero-abluminous exudate in the alveoli, the physical findings of which were those of a pleurisy, a paracentesis thoracalis always giving negative results. The course was protracted, but usually offered good prognosis. The relationship of this splenopneumonia to tuberculosis was not known at that time.

Hutinel[5] in 1911, was the first one in France to point out the frequency with which this splenopneumonia is associated with hilus tuberculosis. Sluka[6] in 1912, described the triangular wedge-shaped infiltration around the hilus glands as characteristic of a tuberculous involvement. Ranke[7] called the areas surrounding a tuberculous structure perifocal inflammations, Tendeloo,[8] collateral

inflammation, and Fraenkel,[9] gelatinous infiltration. Ribadeau-Dumas[10] in 1919, described similar cases under the name of peri-tuberculous infiltrations. Gravinghoff[11] in 1921, reported 3 additional cases of epituberculosis. One of his cases showed complete healing, the second one was still under observation, and the third case came to autopsy one year after the complete disappearance of the epituberculous infiltration of the right upper lobe. The autopsy revealed no tuberculous structures in the right upper lobe; the right hilus showed a calcified gland.

Engel[12] in the same year, reported a number of cases showing what he termed, "paratuberculous lung affections." Some of his cases showed decreased breath sounds over the infiltrate instead of bronchial breathing as reported by the other writers. He also observed cases with an acute onset and with high fever. Of the 3 cases that came to autopsy, one lung showed definite tuberculous involvement, the second case showed "fresh and old pneumonic foci," and the third case, clinically a typical case of epituberculosis, showed grossly no tuberculous structures. The histologic findings were, unfortunately, not given. All of these cases, however, showed a calcified or caseous gland in the hilus on the same side where the epituberculous infiltration was present.

The most important autopsy so far described was that of Epstein[13] who, in 1922, published a typical case of epituberculosis that came to autopsy while the infiltration was still present. The autopsy, performed by Professor Gohn, revealed a large, caseous tuberculous primary focus in the cranial portion of the infiltrate, with many small tubercles surrounding it. There was atelectasis of the remainder of the affected lobe. The histologic examination failed to reveal tubercle bacilli in the atelectatic portions of the lung.

Langer[14] in 1922, reported a typical case of epituberculosis in a child, aged four and a half years, who showed a dense, homogeneous shadow of the left upper lobe, which persisted for over nine months. Four and a half years later the child received $\frac{1}{10}$ mg. tuberculin intravenously which was followed by a high fever, pain over the left upper chest, and by physical and roentgenologic findings of massive pulmonary involvement of the same left upper lobe. This infiltration disappeared fourteen days later. Langer thought that this case proved the specific tuberculous nature of the so-called epituberculosis. Wimberger,[15] Kleinschmidt,[16] Bass and Wessler,[17] Wagner,[18] and Redeker[19] reported additional cases in 1924 and 1926.

In the American medical literature, Gerstenberger and Burhaus,[20] in discussing ultraviolet therapy of extensive pulmonary tuberculosis in infants, reported 7 cases of massive pulmonary involvement —all of whom recovered. Some of their infants even showed roentgenologic evidences of large cavity formations. They exposed their patients to the quartz mercury arc at least three times a week and

it was their impression that they were benefited thereby. The experiences they obtained "forced them to agree with Kleinschmidt, Epstein, Gravinghoff, Engel and others that the clinical syndrome described by Eliasberg and Neuland for differentiating between a tuberculous or a nontuberculous massive pulmonary infiltration is not satisfactory or dependable." They even went so far as to state that "even cavitation might represent a stage of successful, specific immunologic process" of the body against the tubercle bacillus. Stoloff[21] reported a case that most probably belongs to the type of epituberculosis. In 1929, one of us[22] encountered 8 cases of epituberculosis in a follow-up study of 404 tuberculous infants.

Case Reports. During the last two years, we have been conducting a follow-up study in 500 tuberculous contacts and controls among the dispensary children of the Municipal Tuberculosis Sanitarium of the city of Chicago. We encountered 10 typical cases of epituberculosis among these children and we are briefly reporting our observations here.

CASE I.—J. M., colored, aged six years, apparently noncontact to tuberculosis. First seen at the dispensary on February 2, 1929. Chief complaint was poor appetite and a slight cough, especially at night. The patient had had measles and whooping cough; the family history was negative.

The essential physical findings were: Temperature, 100.6°; pulse, 108; respiration, 20. Weight, 47½ pounds; height, 47 inches. Increased vocal and tactile fremitus, with dullness and bronchial breathing over the entire right upper lobe. No râles heard at all. The tuberculin test (dermatubin[23]) was strongly positive. Sputum examination for the tubercle bacillus was negative. The Roentgen ray revealed a dense, homogeneous shadow of the right upper lobe. No changes in the physical findings were noted for three months when the dullness and bronchial breathing began to disappear. Roentgen rays taken at monthly intervals showed a gradual absorption of the infiltrate. The general condition remained good throughout. The temperature, after the initial examination, did not go up above 99°, the appetite was good, and the patient gained 8 pounds in eleven months.

The Roentgen ray taken on October 9, 1929, showed an almost complete absorption of the infiltrate. On January 23, 1930, another tuberculin test (dermatubin) was performed and this was followed by a severe focal, local and general reaction. The physical findings were dullness and bronchial breathing over the entire right side of the lung, and the Roentgen ray examination showed a complete consolidation of the entire right lung. Serial Roentgen ray films, taken one week apart after this reaction, are now beginning to show areas of resorption in the involved right lung.

CASE II.—A. H., aged nine years, colored, apparently noncontact. First seen on April 24, 1929. Chief complaint, cough of few weeks' duration, very slight. Had had measles and diphtheria. Negative family history. Essential findings: Temperature, 99.6°; pulse, 106; respiration, 24. Weight, 50 pounds; height, 51 inches. Dullness and bronchial breathing over the right upper lobe. No moisture. Positive tuberculin test.

Roentgen ray examination showed massive involvement of the right upper lobe. Sputum examination negative for tubercle bacilli (10 times). The general condition of the patient remained good throughout our period of

observation. The patient gained 9 pounds in eleven months. There was a gradual diminution in the density of the area involved which is still progressively diminishing.

CASE III.—M. L., white, aged four years, child adopted at age of two years from St. Johns' Hospital, Springfield, Ill. Nothing known about the parents. Patient was sent in from the Children's Memorial Hospital as a case of pulmonary tuberculosis. First seen on May 17, 1928.

The essential findings: Temperature, 98.4°; pulse, 100; respiration, 22. Weight, 32½ pounds; height, 38¾ inches. The only lung findings noted were harsh breath sounds over the upper left lobe. The dermatubin test was strongly positive. Sputum examination negative for tubercle bacilli. Here again, the general condition remained good and the patient gained 7 pounds in seventeen months. The Roentgen ray plates showed a shrinkage of the tuberculous focus and a shadow density of the left upper lobe resembling that of a calcareous deposit.

CASE IV.—M. B., colored, aged three years. Contact to an open case of tuberculosis (mother) since birth. No complaints—entered the dispensary because mother died of tuberculosis one month previous. First seen on March 24, 1928.

Essential findings: Temperature, 98.6°; pulse, 94; respiration, 22. Weight, 32½ pounds; height, 37½ inches. Dullness and diminished breath sounds over the right upper lobe. Dermatubin test strongly positive. Sputum negative for tubercle bacilli. The patient was followed up until October 17, 1929, when she left the city. The highest temperature noted was 100.6°. Appetite was always good, and on October 17, 1929, her weight was 40 pounds, a gain of 7½ pounds in nineteen months. The Roentgen ray series shows a gradual absorption of the infiltrate going on to complete recovery.

CASE V.—J. B., colored, aged six years, apparently noncontact. Chief complaints: Poor appetite and cough of six weeks' duration.

Essential findings: Temperature, 99°; pulse, 100; respiration, 20. Weight 45 pounds; height, 42½ inches. Dullness of right lower lobe with diminished breath sounds. Dermatubin test strongly positive. Complement-fixation test, negative. Sputum examination negative for tubercle bacilli (15 times). The physical findings and the Roentgen ray films show a gradual absorption of the infiltrate, leaving a center of definite calcification.

CASE VI.—W. T., colored, aged nine years. Apparently noncontact. Chief complaints: Moderate cough of three months' duration. First seen on February 9, 1929.

Essential findings: Temperature, 98.6°; pulse, 118; respiration, 20. Weight, 57 pounds; height, 49½ inches. Dullness and bronchial breathing over the right upper lobe. Dermatubin test is strongly positive. Sputum examination negative for tubercle bacilli (4 times). The Roentgen ray shows a dense, homogeneous involvement of the right upper lobe which is still persisting. The patient's general condition is very good and the patient gained 6½ pounds in one year.

CASE VII.—S. A., aged two years, colored. Contact to an open case of tuberculosis (sister). No complaints. First seen on August 31, 1928.

Essential findings: Temperature, 97.8°; pulse, 100; respiration, 24. Weight, 23½ pounds; height, 32 inches. Dullness and bronchial breathing over the left upper lobe anteriorly. Very strongly positive dermatubin

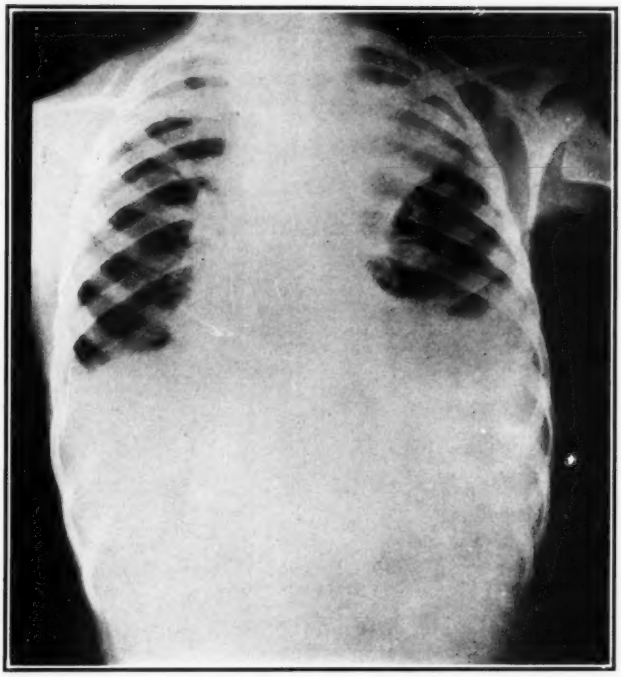

FIG. 1.—Case I. J. M., showing epituberculosis involving right upper lobe, April 27, 1929.

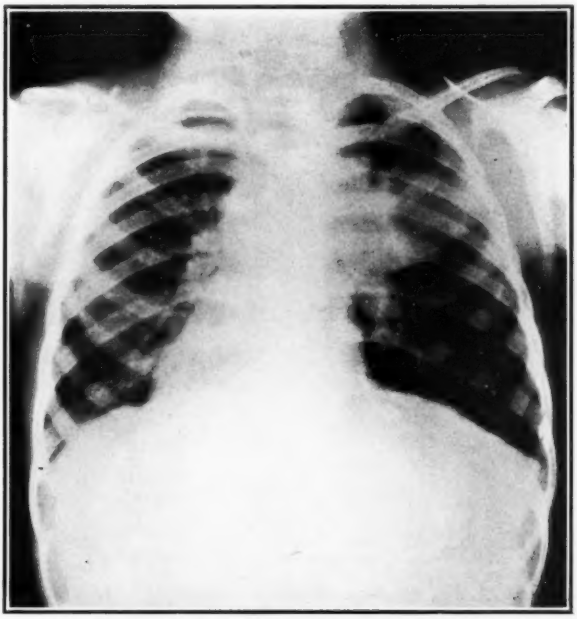

FIG. 2.—Case I. J. M., showing considerable resorption of the area of epituberculosis, October 7, 1929.

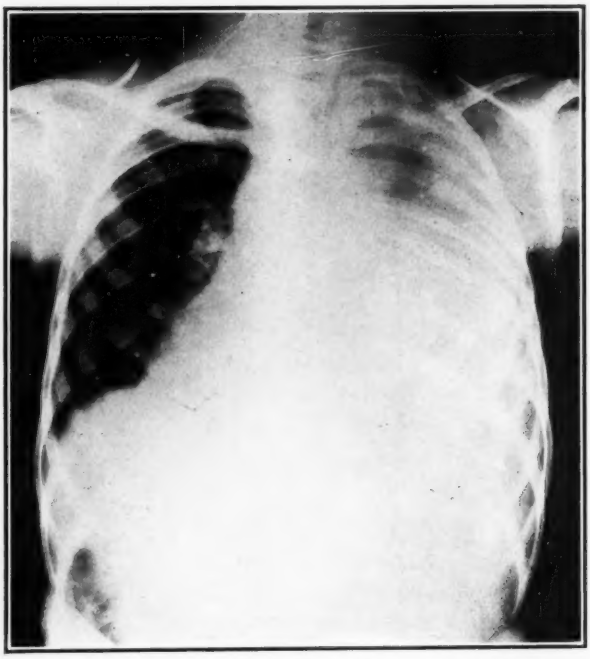

FIG. 3.—Case I. J. M., showing complete involvement of right lung after tuberculin (dermatubin test), January 30, 1930.

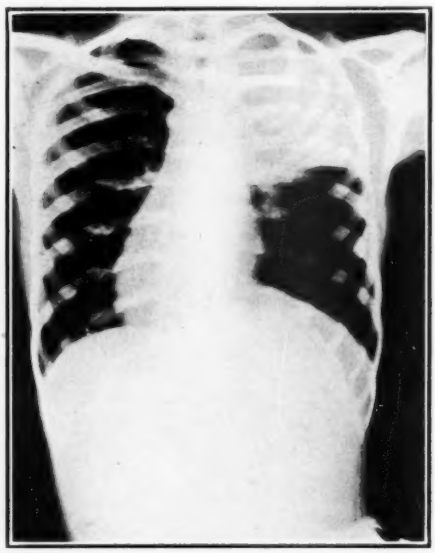

FIG. 4.—Case II. A. H., Showing definitely demarcated areas of epituberculosis involving right upper lobe, May 21, 1929.

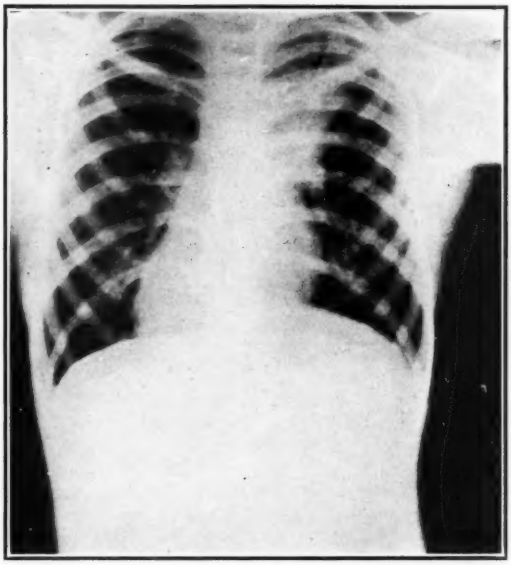

FIG. 5.—Case II. A. H., showing almost complete clearance of area previously involved March 20, 1930.

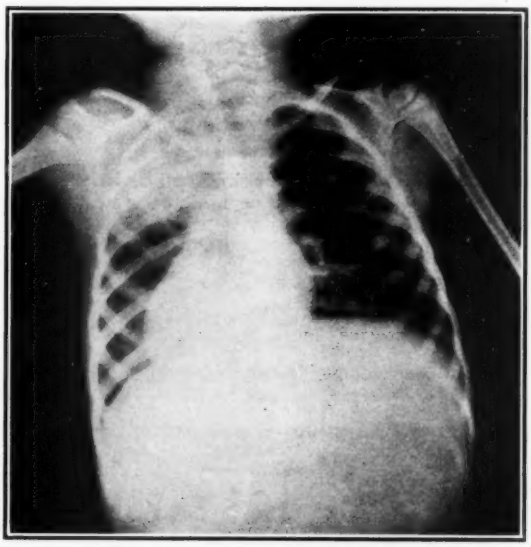

FIG. 6.—Case III. M. L., epituberculosis involving left upper lobe, May 19, 1928.

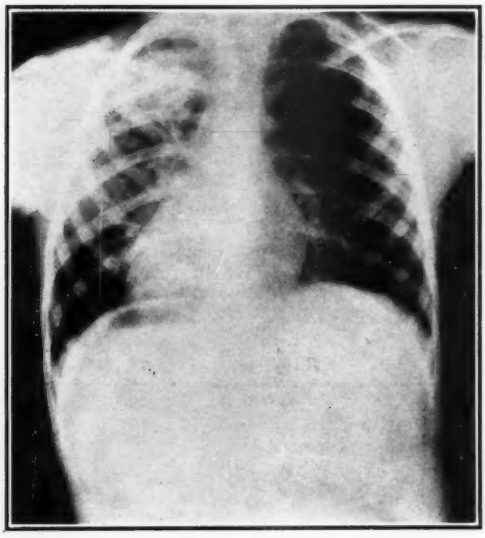

FIG. 7.—Case III. M. L., resorption of epituberculous involvement with shadow density resembling calcareous deposition, January 17, 1930.

test. Sputum negative for tubercle bacilli. The accompanying Roentgen rays show the gradual absorption of the infiltrate. The patient gained 7½ pounds in fifteen months, weighing 31½ pounds on January 30, 1930. The highest temperature recorded is 99° F., and the general condition has always remained good.

Case VIII.—O. M., aged five years, colored. Noncontact. No complaints. First seen on February 26, 1927. Essential findings: Temperature, 99.6°; pulse, 112; respiration, 28. No definite pulmonary findings noted. Dermatubin test strongly positive. Sputum examination negative for tubercle bacilli (twice). The general condition remained good throughout our observation. The patient gained 3 pounds in one year.

Case IX.—W. J., white, aged three years. Apparently noncontact. Chief complaint cough of about two months' duration. First seen on December 11, 1928.

Essential findings: Temperature, 98°; pulse, 100; respiration, 24. Weight, 34½ pounds; height, 39 inches. Dullness and bronchial breathing over the right upper lobe. Dermatubin test strongly positive. Sputum negative for tubercle bacilli. The Roentgen ray film shows dense, homogeneous involvement of the right upper lobe. The general condition was very good throughout the observation, patient gaining 3 pounds in four months. On April 23, 1929, patient developed measles, from which he recovered rapidly. Parents took the patient to California.

Case X.—P. H., aged five years, white. Contact to mother who died of pulmonary tuberculosis two years ago. Chief complaint: Slight cough. First seen on July 6, 1928.

Essential findings: Temperature, 99.4°; pulse, 90; respiration, 20. Weight, 37¼ pounds. Dullness and bronchial breathing over the left upper lobe. Patient is the picture of perfect health. Dermatubin is strongly positive. Sputum examination is negative for tubercle bacilli. Roentgen ray film shows a shadow density involving the left upper lobe. The general condition remained good throughout the observation. Patient weighed 47¾ pounds on January 23, 1930, and the Roentgen rays show a gradual absorption of the infiltrate.

Comment. We have presented briefly the histories and findings of 10 typical cases of epituberculosis. Every one of these cases presented a picture originally described by Eliasberg and Neuland. The onset in our cases was never acute, there was very little fever, and the general condition of our patients was practically always good. All of our patients were ambulatory cases, and every one of them showed a considerable gain in weight during the time under our observation.

It was, indeed, very surprising to find massive pulmonary involvement in patients who oftentimes appeared in perfect health. All of our patients showed definitely positive tuberculin reactions, the sputum was always negative for tubercle bacilli and, in some cases, we examined the sputum on fifteen different occasions.

Our series of stereoscopic plates, showing at first dense homogeneous shadows involving a lobe of a lung, usually the right upper lobe,

and gradually clearing up, leaving in some cases no residue at all, and in others, calcified areas, complete the clinical description of epituberculosis. A study of the blood of our patients, as shown in Table I, gives no additional help in diagnosing this affection, while Table II shows the complement-fixation test for tuberculosis to be of absolutely no value.

TABLE I.—SHOWING THE AVERAGE RED BLOOD CELL, WHITE BLOOD CELL, AND DIFFERENTIAL COUNT IN OUR TEN CASES OF EPITUBERCULOSIS.

Case No.	Hemoglobin, per cent.	Red blood cells.	White blood cells.	Neutrophiles, per cent.	Small lymph, per cent.	Large lymph, per cent.	Monocytes, per cent.	Eosin, per cent.	Basophiles, per cent.
1	65	3,760,000	16,300	79.5	9.0	3.0	7.7 and myelocyte 0.5		
2	75	5,220,000	7,400	26.0	22.0	34.5	14.0	2.5	
3	80	4,165,000	7,450	47.0	11.5	24.5	11.0	4.0	1.0
4	75	4,900,000	8,200	42.0	20.0	31.0	7.0		
5	78	4,390,500	9,265	47.0	32.5	6.5	9.5	4.0	0.5
6	82	5,060,000	6,150	36.0	35.5	15.5	5.0	8.0	
7	72	4,265,000	9,000	41.0	36.0	13.0	7.5	2.5	
8	78	4,270,000	9,250	67.7	9.5	16.0	4.5	2.5	0.5
9	84	5,020,000	13,500	37.5	5.5	51.5	3.5	1.5	
10	70	4,590,000	11,000	69.5	2.0	20.0	7.0 and myeloblasts 0.5	1.0	0.5

200 cells were always counted for differential. Dare method was used for hemoglobin.

TABLE II.—RESULT OF COMPLEMENT-FIXATION TESTS FOR TUBERCULOSIS IN OUR CASES OF EPITUBERCULOSIS.

Case No.	Results.
1	Negative
2	Negative
3	Test not performed
4	Negative
5	Negative
6	Negative
7	Negative
8	Negative
9	Positive
10	Negative

What is the nature of these infiltrations? Are they nonspecific as described by Eliasberg and Neuland, or do they represent specific tuberculous structures as believed by Gravinghoff, Langer, Gerstenberger and others? The autopsies performed do not definitely answer this very important question. The macroscopic and microscopic findings of the case of Eliasberg and Neuland were marked by the intercurrent empyema and bronchopneumonia, and were not reported in detail. The case of Gravinghoff died one year after the complete disappearance of the infiltrate and showed no tuberculous structures except for a calcified gland in the hilum on the affected side. One of Engel's cases showed definite tuberculous tissue but the clinical picture was not typical of epituberculosis. Another of his cases, clinically typical of epituberculosis, showed no tuber-

culous structures except for a calcified hilus gland. Epstein's case came to autopsy while the infiltrate was still present. The autopsy was performed by Professor Ghon and this case throws more light on the nature of the affection than any other case so far reported. The cranial portion of the infiltrate revealed a large caseous tuberculous primary focus, surrounded by many small tubercles. The remainder of the lung infiltrate was atelectatic and showed no tuberculous structures histologically.

Our Case I is unusual in that an infiltration of the whole of the right lung followed a tuberculin test after the original infiltrate had practically disappeared. This is the second case on record where the infiltrate reappeared following a tuberculin test. Our case differs, however, from Professor Langer's case in that the infiltrate, although now showing definite areas of absorption, is still present two months after the tuberculin test. The infiltrate, in our case, is progressing the usual, prolonged course of an epituberculous infiltrate. In Professor Langer's case the infiltrate disappeared within fourteen days. Our case and that of Professor Langer point most strongly to the infiltrate being intimately associated with the tubercle bacillus. It is at least a tuberculotoxic reaction on a specific tuberculous soil. Whether this infiltrate is histologically a tuberculous structure, or whether it consists of nonspecific inflammatory elements surrounding a tuberculous focus, or whether it represents an atelectatic portion of the lung due to the blockage of the return lymphatic circulation by a swollen tuberculous hilum gland or other focus, still remains an open question. Our clinical experience and the few autopsies reported in the literature seem to show that pathologically epituberculosis may, in some cases, represent a nonspecific, collateral inflammation, in others a large atelectatic area and, perhaps, in still others the infiltrate may be a definite tuberculous structure which may go on either to calcification or rarely to caseation and cavitation.

We feel that clinically these cases represent a definite entity, and in the great majority of cases, can be definitely diagnosed and differentiated from tuberculous pneumonias and chronic, nonspecific pneumonias. We feel that Eliasberg and Neuland deserve much credit for calling the attention of the medical profession to this type of lung affection, even though experience has shown that it is not always so easy to differentiate epituberculosis from tuberculous pneumonias. In the past, a tuberculous child with massive pulmonary involvement was always given the death verdict. Now we know that this massive pulmonary involvement oftentimes represents a beneficial, successful immunologic reaction of the body toward the destructive advances of the tubercle bacillus.

Conclusions. 1. Ten typical cases of epituberculosis in children have been studied clinically and roentgenologically for a period of about two years.

2. All of our cases were tuberculous children who presented massive pulmonary involvement, which either completely disappeared or is still undergoing resolution.

3. In one of our cases which had undergone resorption, an infiltration of the right lung followed a tuberculin reaction.

4. The epituberculous infiltrate is intimately associated with the reactions of the tubercle bacillus or of its toxins.

5. It is not clear whether the epituberculous area is a collateral inflammation or an atelectasis, the result of blockage of an enlarged hilum glandular process, or a truly tuberculous parenchymal involvement, or any of these in a given case.

NOTE.—The authors appreciate the assistance in the dispensary supervision of these cases by Drs. Harry H. Freilich, Saul Soloway and the late Dr. Joseph S. Cohn.

REFERENCES.

1. Eliasberg and Neuland: Die Epituberkulose Infiltration der Lunge bei Tuberkulosen Säuglingen und Kind, Jahrb. f. Kinderh., 1920, **93**, 88.
2. Eliasberg and Neuland: Zur Klinik der Epituberkulose and Gelatinosen Infiltration, Jahrb. f. Kinderh., 1921, **94**, 102.
3. Grancher: Proceeding Société Medicale des Hôpitaux, 1883, **8**, 13.
4. Bourdel: De la Splenopneumonie, Paris, 1886.
5. Hutinel: Les reactions broncho-pulmonaires dans les adenopathies mediastines, Gas. des hôp., 1911, **84**, 76.
6. Sluka: Die Hilustuberkulose des Kindes in Roentgenbild., Wien klin. Wchnschr., 1912, **7**, 140.
7. Ranke: Zur Diagnose des Rindlichen Tuberkulose, München. Med. Wchnschr., 1914, **27**, 2099.
8. Tendeloo: Allgemeine Pathologie, Berlin, J. Springer, 1919, pp. 409 and 416.
9. Fraenkel: Pathologische Anatomie, Kaufman's I, p. 341, 1922, Berlin, V. W. V.
10. Ribaldeau-Dumes: Les reactions perituberculeuses die poumon de l'enfant, J. de méd. et de chir. prot., 1919, **90**, 933.
11. Gravinghoff: Zur Kenntnis der Epituberkulose Infiltration, Monatschr. f. Kinderh., 1921, **21**, 447.
12. Engel: Ueber Paratuberk. Lungenerkrankungen, Berlin, Klin. Wchnschr., 1921, **31**, 877.
13. Epstein: Zur Klinik der Epituberkulose Infiltration der Rindlichen Lunge, Jahrb. f. Kinderk., 1922, **97**, 99.
14. Langer: Die Spezifität Ruckbildunsfähiger Lungeninfiltrate bei der Rindlichen Tuberkulose, Ztschr. f. Kinderk., 1922, **34**, 142.
15. Wimberger: Verhand. d. Deutch. Gesellsch. f. Kind,Monatschr f. Kinderh., 1925, **29**, 409.
16. Kleinschmidt: Beit. z. Klin. d. Tuberk., 1926, **61**, 330.
17. Bass and Wessler: Die Besonderlichkeiten der Roentgen Thorax Diagnose in Kindesalter, Jena, 1924, p. 91.
18. Wagner: Mitteil d. Gesell. f. inn. Med. u. Kinderh. in Wien, 1926, **19**, 364.
19. Redeker: Ueber die exudative Lungeninfiltrate, Beitz. z. Klin. d. Tuberk., 1926, **59**, 588.
20. Gerstenberger and Burhaus: Treatment of Extensive Pulmonary Tuberculosis with Ultraviolet Rays, Am. J. Dis. Child., 1927, **33**, 54.
21. Stoloff: Acute Massive Atelectasis of the Lung Complicating a Fresh Tubercular Primary Complex, Am. J. Dis. Child., 1928, **35**, 239.
22. Gasul, B. M.: The Prognosis of Tuberculosis in Infants, Am. J. Dis. Child., 1929, **37**, 909.
23. Goldberg, B. and Gasul, B. M.: A Comparison of the Dermatubin, Pirquet, Moro and Mantaux Tests. (To be published.)

THE PROTECTIVE POWER OF THE PLEURA.

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There is a striking similarity between the peritoneum and the pleura. This latter tissue has not as yet received its proper consideration. Both these tissues are morphologically related: They develop from a common ancestor. They cover the intrathoracic and intraäbdominal organs and afford the necessary protection to these organs. Under normal conditions they prevent friction by the production of a lubricating fluid over the surface of each organ. In case of inflammation (be it bacterial, physical or chemical in origin) the peritoneum, as well as the pleura, produces a fibrinous exudate which patches the local injury and in more severe types it plasters the respective organ to an adjacent normal organ or the adjacent wall.

The lung is surrounded by the visceral pleura. One may consider the tissue as a part of the lung tissue. Actually, however, it is not related to the structure of the lung and acts only as a protective cloak. Under normal conditions it is made up of a few layers of cells and these have the power of preventing any leakage of air or fluids from the lung into the pleural cavity. This tissue is so thin and transparent that it makes a very useful window through which to watch the structure of the functioning lung. In certain species of lungs, as for instance the beef lung, where there is a great tendency to divide into lobules, the pleura is seen to extend into the interlobular space. In other species as the sheep, the dog, and to some extent in man, there is a lesser tendency to lobulation and the pleura appears as a uniform sheet covering the lung tissue. The pleura is apparently just merely attached to the lung because if the intraälveolar air pressure is raised to a point beyond the strength of cohesion between the lung and the pleura, the latter separates from the lung and forms an air bulla. If this increased pressure persists, the air will now undermine the bullous pleura and cause a greater separation. If this rise in intrapulmonic pressure is too rapid, the air bulla, instead of enlarging, will rupture and cause a pneumothorax. It requires a pressure of 60 to 100 mm. of mercury to produce this phenomenon. It can be produced by introducing the compressed air from a tank intratracheally or by the use of an air-tight mask attached snugly to the nose and mouth of the dog.

The pleura limits the lung volume to a certain maximum. The lung tissue is very elastic and has a power of expansion much greater

than the total volume allowed for by the pleura. It is this reserve elasticity that allows the lung to stretch the pleura to a drumlike tension, and when a break occurs then the separated parts give way on either side of the rupture, allowing a lateral stretching of the lung but no herniation of the lung through the pleura. The pleura is so air-tight that even at a pressure of 100 mm. of mercury above atmospheric pressure no leakage of air occurs. Slight injuries to the lung such as needle pricks or small incisions are healed over without much discomfort to the subject. Following such a wound the lung-tissue juices promptly plug up the opening and the pleura promptly covers it over with new cells or induces an adhesion of this part of the lung to the chest wall. This protective power cannot be utilized if the wound has injured the larger bronchioles or larger vessels whereby a bronchial fistula or a severe hemorrhage may result.

The osmotic function of the pleura is quite important and applies primarily to the colloidal fluids present in the lung. These fluids usually do not pass through the pleural lining. Crystalloids, and water, on the other hand, may find their way into the pleural sac under two conditions, namely, the accumulation of a large amount of such a fluid and the increase of intraälveolar pressure. Water or normal salt solution may be used to fill up an extirpated lung with the heart attached to it. This water for the most part will find its way toward the lower lobe and will begin to appear much like perspiration on the surface of the pleura. This is probably the mechanism of transudation associated with chronic passive congestion of the lung in decompensation of the heart. When the intrapulmonic pressure is increased by injecting this water under pressure, drops of water accumulate very rapidly at the tip of the lung. Bloody fluids now are seen to come out under pressure from the severed systemic vessels leading to the heart or from the opened heart. The flow of the water is more noticeable when the pulmonary vessels are severed at a point before they enter the lung. When air is now blown into the lung at a pressure of 20 to 40 mm. of mercury, the flow of water continues from the vessels and the tip of the lung. In a few minutes the upper lobes begin to show crepitation and gradually the rest of the lung becomes air-containing. The process of forcing water out of the lung by increasing the intrapulmonic pressure is not similar to the expansion seen in a consolidated pneumonic lung where the intraälveolar exudate is colloid and contains fibrinous strands. This fibrin as it contracts, pulls the alveolar walls together and lessens the alveolar volume. The consolidation is due to the presence of exudate as well as the diminution of the volume of each alveolus due to the contraction of the fibrinous deposits. It is perhaps for this reason that with only a slight increased intrapulmonic air pressure (20 to 35 mm. Hg.) we can see the lung expand to its normal volume without any fluids leaking out through the pleura.

Another means of determining the water-tight effect of the pleura can be demonstrated by immersing a normal formalin-fixed lung under water. It will be noticed that water enters the lung only through the bronchi. If, however, the pleura is stripped off carefully so as not to expose any larger bronchioles, the water will run into the lung both from the bronchus and the exposed, capsule-free lung. One can squeeze such a lung to get all the residual air and then dip it in water. In a few minutes it will absorb enough of water to expand to its normal volume much in the manner of a sponge.

In inflammation of the lung the pleura plays the same protective rôle as the peritoneum in the abdominal cavity. A localized pleurisy is usually present in the region of the inflammatory reaction of the lung. If the inflammation is sufficiently extensive, adhesions usually form between the lung and the chest wall in an effort to localize the lesion by immobilizing that part, and in the case of perforation into the pleural cavity by preventing a pneumothorax or a general empyema. Pleurisy with effusion associated with pneumonia or respiratory influenza should be looked upon much in the same manner as that of general peritonitis. Here the protective power of the pleura is temporarily overcome and a tendency to localization occurs as soon as the virulence of the infecting organism is lowered or the patient's resistance is raised.

Summary. 1. The pleura and peritoneum are anatomically and physiologically related. They both act as protective cloaks of their respective organs.

2. Normally the pleura and peritoneum prevent friction by keeping in a state of lubrication the organs that they cover. Under pathologic conditions they tend to wall off the underlying infection by the production of adhesions.

3. The pleura is a water-tight and air-tight covering of the lung. It protects the lung from overdistention. It normally prevents fluids from going from the lung into the pleura and *vice versa*. Air is not allowed to escape from the lung into the pleura except when the pleural lining is injured.

4. An intrapulmonic air pressure of over 60 mm. of mercury will cause a separation of the pleura from the lung and result in an air bulla.

5. Pleural effusion associated with pneumonia or influenza may be regarded in the same light as peritonitis following gastrointestinal inflammation. There is a tendency on the part of the pleura to localize the lesion or protect the rest of the lung by the production of adhesions.

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THE OCULAR MANIFESTATIONS OF SYMPATHETIC NERVOUS SYSTEM HYPERACTIVITY IN CONDITIONS OTHER THAN EXOPHTHALMIC GOITER AND ESPECIALLY IN ESSENTIAL HYPERTENSION.

"Lidspasm:" A New Eye Sign.

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The classical descriptions of exophthalmic goiter have considered exophthalmos and the eye signs with which it is customarily associated, as a frequent, although not necessarily a constant, phenomenon of Graves' syndrome. Little attention, however, has been directed to the fact that these ocular manifestations appear not only in exophthalmic goiter, but also in what seem to be, on superficial consideration, wholly unrelated clinical syndromes.

The apparent frequency with which exophthalmos and its associated eye signs were met in routine physical examinations of patients with hypertension and various conditions other than exophthalmic goiter prompted further investigation in this direction.

Historical. The historical aspect of this question which concerns itself with the mechanism involved in the production of these ocular phenomena, as well as with their occurrence in conditions other than Graves' syndrome, is an interesting one.

Early Theories. It was not long after the early descriptions of exophthalmic goiter that theories concerning the mechanism of its production were naturally considered. Of these, increase in retrobulbar fat and increased periorbital vascularity were most favored. Both of these theories had their advocates, but it was soon recognized that each had its limitations, some of them insurmountable.

The clinical observations that the degree of exophthalmos could vary in intensity from time to time in the same patient dealt the fatal blow to the hypothesis which considered an increase in retrobulbar fat as the essential feature. This knowledge, in spite of the relative frequency with which an increase in retrobulbar fat was demonstrated during postmortem examinations, soon established the latter as a manifestation of secondary importance complicating chronic exophthalmos.

Trousseau[1] (1865) and Filehne[2] (1879) were among the early advocates of the increased vascularity theory. In his experimental production of exophthalmos, Filehne[2] noticed that enucleation of normal eyes in rabbits was unattended by the profuse hemorrhage

which took place when a similar operation was performed on an exophthalmic eye; Trousseau[1] reasoned that the rapid development of exophthalmos in acute exacerbations of Graves' syndrome was dependent upon engorgement of the orbital bloodvessels.

ANATOMIC ASPECTS. This theory, in its turn, has given way to the explanation based on anatomic and physiologic data. This became possible after Müller,[3] MacCallum and Cornell,[4] and subsequently Landström,[5] described the smooth muscle fibers which extend about the eyeball and are attached to the eyelids as well as the anterior orbital fascia. Müller[3] (1885) described very briefly three groups of plain muscle fibers: one bridging over the infra-orbital fissure and one in each eyelid, running vertically from the fornices of the conjunctiva to the superior and inferior tarsal plates respectively. By means of dissection and histologic studies, MacCallum and Cornell[4] (1904) were able to demonstrate a conical mantle of smooth musculature about the eyeball continuous anteriorly with the musculature of the lids, and forming abundant attachments about the margin of the orbit. This musculature then passed backward to end about the foramen, through which the optic nerve entered the orbit.

In reviewing Müller's work, Landström[5] (1907) suspected the inadequacy of these muscles, both from their size and position, in being wholly responsible for the production of exophthalmos and the associated eye signs. This, together with the inadequacy of the existing theories, led Landström to a more intensive histologic study of the orbital contents. By means of serial sections in different planes, he demonstrated a well-developed cylinder of plain muscle arising from the septum orbitale anteriorly and inserted just posterior to the equator of the eyeball. The eye signs of exophthalmic goiter now became more readily explicable on the basis of the accumulated anatomic discoveries of Müller, MacCallum and Cornell, and Landström.

PHYSIOLOGICAL ASPECTS. It remained, however, for the experimental physiologist to point out conclusive evidence in favor of this mechanism for the production of exophthalmos and the associated eye signs; further proof of a similar character was suggested by experience in the surgery of cervical sympathetic ganglia and by analogy with a characteristic clinical syndrome (Horner).

Exophthalmos has been produced experimentally on numerous occasions. The earliest attempt is recorded by Filehne[2] (1879), who originally produced it by incision or cauterization of the upper quarter of the inner portion of the corpora restiformia; Bienfait[6] (1890) was able to confirm Filehne's observations with further experimental lesions of the restiform bodies. Additional evidence of a similar nature was offered by Mendel[7] (1892), who reported a postmortem examination in exophthalmic goiter which revealed an atrophy of one restiform body.

As one would expect, the smooth musculature of the orbit (Müller, MacCallum and Cornell, and Landström) is abundantly innervated by the sympathetic nervous system, and its state of tonicity is constantly maintained by the latter. On the basis of this knowledge, Bernard[8] (1862), Benard[9] (1882), Langley and Sherrington[10] (1891) and Jonnesco[11] (1900) demonstrated the production of exophthalmos and widened palpebral fissures by means of stimulation of the cervical sympathetics, and reported their results unequivocally. MacCallum and Cornell[4] (1904) contributed important and substantial observations of a similar character. After removing the roof of the orbit and the orbital fat in dogs, they found that electrical stimulation of the cervical sympathetics produced great exophthalmos. During the experiment they observed peristaltic waves passing backward throughout the tissue surrounding the eyeball, and subsequent studies (*vide supra*) revealed the smooth musculature responsible for the peristaltic waves, exophthalmos and widened palpebral fissures. By further ingenious experiments, they demonstrated that the exophthalmos produced by cervical sympathetic stimulation was entirely independent of vascular bed changes in the orbit and directly dependent upon sympathetic nervous system stimulation of the smooth musculature. In 1915 Cannon, Binger and Fitz[12] reported unmistakable exophthalmos resulting from phrenicosympathetic anastomosis in cats and, although subsequent attempts to confirm this experiment have been unsuccessful, the original positive results are worthy of serious consideration.

Clinical Aspects. In 1865 Trousseau[1] emphasized the relation of the superior cervical sympathetic ganglion to the production of exophthalmos, and Edmunds[13] (1895) later advocated extirpation of the superior cervical sympathetic ganglion for the relief of distressing exophthalmos. Subsequent surgery (Jaboulay,[14] Jonnesco,[15] Balacescu,[16] Kocher[17] and Mayo[18]) substantiated the practicability of Edmund's original suggestion.

The clinical syndrome (Horner) occasionally found complicating fractures of the cervical vertebræ with injury to the cervical sympathetics, and a similar condition produced experimentally (Langley and Sherrington,[10] 1891), by sectioning the cervical sympathetic cord, is characterized by enophthalmos, pseudoptosis and myosis. Special sympathetic vasomotor disturbances usually accompany these changes, and all of them are obviously dependent upon interference with the activity of the sympathetic nervous system.

Eye Signs of Sympathetic Nervous System Hyperactivity. The available evidence, therefore, points to hyperactivity of the sympathetic nervous system as the factor responsible for the production of exophthalmos through spasm of the smooth muscles described by Müller, MacCallum and Cornell, and Landström. In the same way, the eye signs frequently found associated with exophthalmos or alone in exophthalmic goiter are no doubt produced

by means of a similar mechanism (von Graefe,[19] Landström[5]). Although von Graefe recognized the coördination which normally exists between movements of the upper eyelid and the eyeball when the axis of vision is elevated or depressed, he pointed out only those instances in exophthalmic goiter (von Graefe[19]) where he noted failure of the upper lid to follow the downward movement of the eyeball. Subsequently, Kocher[20] (1910) described the retraction of the upper lid when the patient looked intently at an object. Referring to exophthalmic goiter and disturbances of innervation of the eyelids "in the domain of reflex activity . . . and of the arbitrary movements of coördination," Stellwag[21] (1873) writes that "to the first category belongs one of the most constant symptoms usually present from the beginning, namely, the wide opening of the interpalpebral fissure and the incompleteness and rarity of the rhythmic movements of the lids. The gaping of the palpebral fissure is usually so large that quite a wide zone of sclera is exposed above and below the corneal margin. The rhythmic movement of the lids is often entirely absent for several minutes, is also generally very incomplete and is replaced by a slight drawing inward and by a weak, screwlike rotation of the edge of the lid. This symptom, in connection with the wide opening of the palpebral fissure gives to the physiognomy of the patient the peculiar hardness and staring appearance which is mentioned by so many authors."

In speaking of the action of the levator palpebræ superioris, Dalrymple[22] (1834) states that "Its action is to raise the upper lid, to uncover the globe of the eye by drawing the tarsal cartilage beneath the margin of the orbit and at the same time it slightly protrudes the globe. In this last action it indirectly depresses the lower eyelid, inasmuch as the protrusion of the globe causes the lower lid to slide off its anterior convexity, and thus opens the eye to a greater extent, as in the act of staring." A modification of the latter in the form of inequality of the palpebral fissures has been reported, but its relative frequency has never been emphasized.

Lidspasm: A New Eye Sign. There remains one other eye sign to which reference has not been made hitherto. Its value lies in the fact that it is often present when the von Graefe is absent, although not necessarily positive when the von Graefe can be elicited. It is determined in a manner similar to that for the von Graefe, but in the reverse manner. After the patient watches the object reach the lowest point of the arc and the von Graefe sign has been completed, the object retraces its former path, in the upward direction. The upper eyelid is now retracted in advance of the moving eyeball, and a rim of white conjunctiva appears above the cornea if the "lidspasm" sign is positive. In some cases the rim of white conjunctiva does not appear, but there is sufficient dissociation of movement between the upper eyelid and the eyeball to designate the eye sign positive. Judging from the character of the new eye

sign and the manner in which it is elicited, its mechanism appears to be similar to that suggested for the von Graefe, and would, therefore, be dependent upon hyperactivity of the sympathetic nervous system with spasm of the smooth muscle in the upper eyelid.

CLINICAL MATERIAL AND PROCEDURE. The suprising frequency with which exophthalmos and its associated eye signs were met in routine physical examinations of patients with hypertension, obviously not suffering from exophthalmic goiter, prompted further investigation in this direction.

The Medical Out-door Department of the Peter Bent Brigham Hospital was particularly well suited to this type of work. Patients of every description are examined routinely, and in reality represent a cross-section of illness in adults of limited financial means. By far the largest amount of data was gathered on the female medical service and only a negligible small per cent of males were included.

Only 494 patients of the total number examined were eligible for this clinical study. All instances in which the thyroid gland might possibly be considered a complicating factor were automatically omitted. A sufficient number of basal metabolism determinations were carried out and found normal in the more difficult instances where the intensity of the symptoms and signs were of such a nature as to make exophthalmic goiter a distinct possibility. The surprising number of these determinations which were either normal or unusually low led to further study concerning the significance of exophthalmos and the associated eye signs of sympathetic nervous system hyperactivity.

This study, therefore, included 258 consecutive cases of essential hypertension, and 236 consecutive patients without hypertension were included to form some basis for relative comparison. Each patient was examined routinely, and special note made of age, clinical diagnosis, blood pressure and eye signs. The latter included bilateral and unilateral exophthalmos, von Graefe, Kocher, inequality of palpebral fissures, unequal pupils and the new eye sign "lidspasm." All doubtful signs were reported negative.

It was found that inequality of palpebral fissures could be determined accurately on inspection if note was made of the anatomic relation of the margin of the upper eyelid to the upper margin of the pupil. Exophthalmos was not measured by an exophthalmometer, but was determined by inspection. It was found by experience that unilateral exophthalmos was invariably accentuated if the patient looked in the upward direction. In the latter position, protrusion of the lower one-half of the eyeball became relatively more marked on the affected side. It is with full cognizance of the limitations in accuracy, dependent upon the personal equation, that the observations on exophthalmos are submitted. A colleague made an independent observation in a large number of the examinations, and only those cases which were substantiated in this manner are reported positive for either unilateral and bilateral exophthalmos

or unequal palpebral fissures. And finally, it was discovered that the von Graefe and lidspasm signs were more likely to be elicited with the patient in the vertical than in the horizontal position. In some instances they could be made to disappear by simply changing the patient from the former position to that of the latter.

CLINICAL DATA. The clinical data, gathered in this manner, has been summarized in the following paragraphs.

Hypertension is most prevalent in the sixth decade, and there is little significant difference in age frequency among those with or without eye signs. The peak of the curve for patients without hypertension (correlating frequency and age) lies in the fifth decade. Further, it is obvious that those without eye signs are by far in the majority in the group of patients without hypertension and that eye signs appear at an earlier age than in the group of patients with hypertension:

Age.	Per cent of 258 patients with hypertension.		Per cent of 236 patients without hypertension.	
	With eye signs.	Without eye signs.	With eye signs.	Without eye signs.
10+	0.0	0.38	1.60	6.7
20+	0.0	0.38	3.30	13.9
30+	1.9	1.10	4.60	19.0
40+	10.8	11.20	5.00	24.5
50+	15.1	20.60	5.00	8.8
60+	17.0	12.00	0.08	4.2
70+	2.7	5.80	0.00	1.2
80+	0.7	0.00	0.00	0.0

Of 258 patients with hypertension examined, 125 (44 per cent) had one or more of the eye signs mentioned above, with the exception of bilateral exophthalmos, which is reported independently (*vide infra*). Among 236 patients without hypertension, 49 (21 per cent) had one or more of the same eye signs.

Among the patients with hypertension the eye signs occurred in 29 different combinations and the number of eye signs in a single individual varied from one to five:

	Per cent of 125 patients with eye signs.	Per cent of all with hypertension (258).
70 patients had 1 (70 eye signs)	56.0	23.2
34 patients had 2 (68 eye signs)	27.0	13.1
10 patients had 3 (30 eye signs)	8.0	3.8
7 patients had 4 (28 eye signs)	5.6	2.7
4 patients had 5 (20 eye signs)	3.2	1.5

Total number of eye signs, 216.

In the group without hypertension there were nineteen different combinations of the eye signs, and the number in a single individual also varied from one to five:

	Per cent of 49 patients with eye signs.	Per cent of all without hypertension (236).
33 patients had 1 (33 eye signs)	67.3	13.9
10 patients had 2 (20 eye signs)	20.4	4.2
4 patients had 3 (12 eye signs)	8.1	1.6
1 patient had 4 (4 eye signs)	2.0	0.04
1 patient had 5 (5 eye signs)	2.0	0.04

Total number of eye signs, 74.

Bilateral exophthalmos was found about three times as frequently among patients with hypertension (15.5 per cent) as compared with individuals without hypertension (5.9 per cent). In the former it was associated with combinations of other eye signs in 8.9 per cent and in the latter in 2.5 per cent of the cases.

The frequency with which the individual signs occurred in patients with hypertension are tabulated as follows—the relative frequency of each eye sign was especially emphasized by the fact that each patient might have two or more in various combinations:

Signs.	Number recorded in 258 patients with hypertension.	Per cent of 125 patients with eye signs.	Per cent of all with hypertension (258).
Unequal palpebral fissures	73	58.0	28.2
Unilateral exophthalmos	38	30.2	14.7
Von Graefe	36	28.4	13.7
Kocher	36	28.4	13.7
Lidspasm	26	20.4	10.0
Unequal pupils	7	5.6	2.7
Total number of eye signs	216		

Unilateral exophthalmos was found associated with a wide palpebral fissure on the same side in 24 of these cases.

Among the patients without hypertension the frequency with which the individual eye signs of sympathetic nervous system hyperactivity appeared, occurred as follows:

Signs.	Number recorded in 236 patients without hypertension.	Per cent of 49 patients with eye signs.	Per cent of all (236) without hypertension.
Unequal palpebral fissures	22	44.0	9.3
Von Graefe	16	32.6	6.7
Unilateral exophthalmos	11	22.4	4.6
Lidspasm	10	20.4	4.2
Kocher	10	20.4	4.2
Unequal pupils	5	10.2	2.1
Total number of eye signs	74		

Unequal palpebral fissures are, therefore, the most common, and unequal pupils the least frequent of all eye signs in both groups.

The relative frequency of eye signs seems to be directly proportional to the degree of systolic hypertension. Blood-pressure readings were grouped in the following manner for statistic and illustrative purposes:

Blood pressures.	Per cent of 125 patients with hypertension and eye signs.	Per cent of 133 patients with hypertension but without eye signs.
$\frac{200+}{100\pm}$	41.6 (52 patients)	28.5 (38 patients)
$\frac{140 \text{ to } 198}{100+}$	22.4 (28 patients)	24.0 (33 patients)
$\frac{140 \text{ to } 198}{100-}$	36.0 (45 patients)	46.6 (62 patients)

If the eye signs are grouped individually according to the pressures with which they were found associated in the 125 patients with hypertension, it is evident that unequal palpebral fissures and unequal pupils are most often detected with the lower pressures. In spite of the fact that there is a decided predominance of patients with systolic blood pressures below 200, the remaining eye signs (unilateral exophthalmos, von Graefe, Kocher and lidspasm) show a marked tendency to appear associated with blood pressures whose systolic level is above 200:

Blood pressure.	Unequal palpebral fissures, per cent.	Unilateral exophthalmos, per cent.	Von Graefe's sign, per cent.	Kocher's sign. per cent.	Lidspasm sign, per cent.	Unequal pupils, per cent.
200+ / 100±	17.6	14.4	14.4	12.0	9.6	1.60
140 to 198 / 100+	12.0	8.0	3.2	4.8	4.0	0.08
140 to 198 / 100−	24.8	11.2	11.2	10.4	6.4	3.20

The patients with hypertension as well as those without hypertension who were examined on more than one occasion revealed the remarkable manner in which these sympathotonic signs could appear and disappear again on subsequent examinations. An example is abstracted at this point. This patient, with a definite history of hypertension, was seen on seven consecutive visits to the Out-door Department of the Peter Bent Brigham Hospital. Her general state of nervous tension seemed to have more relation to the intensity and number of the eye signs than did her blood-pressure level:

Date.	Blood pressure.	Eye signs.
Nov. 27, 1929	190/105	Von Graefe; bilateral exophthalmos.
Dec. 11, 1929	210/110	Von Graefe; bilateral exophthalmos; unequal palpebral fissures.
Dec. 23, 1929	152/80	Bilateral exophthalmos; unequal palpebral fissures.
Dec. 30, 1929	196/110	Von Graefe; lidspasm; Kocher; bilateral exophthalmos; unequal palpebral fissures.
Jan. 6, 1930	170/110	Von Graefe; Kocher; bilateral exophthalmos; unilateral exophthalmos, right, unmistakable; unequal palpebral fissures.
Jan. 13, 1930	188/92	Von Graefe; bilateral exophthalmos.
Jan. 18, 1930	180/100	Bilateral exophthalmos.

The diagnoses which represented the clinical condition of the 49 patients without hypertension but with eye signs are outlined at this point. The striking preponderance of the diagnosis "neurasthenia," the occurrence of so many patients with hypotension

and the relatively large number of neurologic and arthritic conditions seem worthy of special note.

24 with neurasthenia (functional disease); 6 had hypotension.
6 with chronic atrophic arthritis; 1 had hypotension.
5 with hysteria; 1 had hypotension.
4 with petit or grand mal; 2 had hypotension and 1 had duodenal ulcer.
2 with postencephalitic Parkinson's syndrome; 1 had hypotension.
2 with pulmonary tuberculosis; 1 had hypotension.
2 with duodenal ulcer; both had hypotension.
1 with primary familial muscular atrophy; also had hypotension.
1 with diabetes mellitus; also had hypotension.
1 with paroxysmal auricular fibrillation.
1 with hypotension.

A systolic blood pressure constantly below 110 mm. was considered a hypotension. Seventeen patients (35.6 per cent) of those with eye signs had clinical hypotension. Only 13 per cent had hypotension in the group without eye signs.

Discussion. At the present state of our knowledge certain facts are known concerning the anatomic distribution of the sympathetic nervous system and the signs and symptoms of its hyperactive state. The latter may be expressed either subjectively or objectively. The subjective manifestations include various types of nervousness, palpitation, emotional and vasomotor instability (peripheral vasoconstriction and dilatation). The objective signs of sympathetic nervous system hyperactivity may be detected through its influence on tonicity of musculature (tremor), cardiac rate (tachycardia), secretion of the sudoriferous glands (sweating) and the ocular manifestations of exophthalmos, lidlag, lidspasm, Kocher's sign and Dalrymple's sign.

A syndrome consisting of these signs and symptoms may be termed sympathotonia for convenience of reference. One must recognize, however, that as a general rule the latter is just a partial manifestation of a more profound autonomic disturbance. Although relief of the subjective manifestations are of immediate importance to the patient, he may well exaggerate their discomfort. It is the objective findings which point with reasonable accuracy to the actual state of tonicity and activity of the sympathetic nervous system.

During the course of this investigation, which was directed principally at the eye signs of sympathotonia, several broad generalizations naturally suggested themselves.

The most obvious of these was the widespread evidence of sympathotonia. Its occurrence in exophthalmic goiter has been

accepted as classic as well as a usual, although by no means constant, part of the syndrome. However, the intensity and frequency with which the eye signs of sympathotonia occurred in essential hypertension was apparently unsuspected, and its recognition suggested the possibility of a fundamental sympathetic disturbance common to both maladies.

The occurrence of exophthalmos in conditions other than exophthalmic goiter, and independent of mechanical production, was first reported by Sattler[23] (1885) in 3 cases. He pointed out its "symptomatic importance as an occasional attendant of hemorrhagic forms of retinitis occurring in connection with altered and increased general arterial pressure, the result of cardiac, renal and hepatic lesions." A slightly more extensive report of 16 cases of chronic nephritis was offered by Barker and Hanes[24] (1909). They found:

> Von Graefe positive in 68.7 per cent of 16 cases.
> Stellwag positive in 81.3 per cent of 16 cases.
> Moebius positive in 43.7 per cent of 16 cases.
> Unequal pupils in 31 per cent of 16 cases.
> Albuminuric retinitis in 50 per cent of 16 cases.

They further noted that there was a coincident decrease in exophthalmos with a decrease in blood pressure, and believed that the hypertension as well as the exophthalmos were due to the same cause rather than dependent on each other. Our own observations seem to substantiate this opinion. In commenting upon this report, Thayer[24] confirmed the data presented by Barker and Hanes from his own clinical experience.

This new conception, of a sympathetic disturbance common to both exophthalmic goiter and hypertension, seemed of still greater significance when it was found that 21 per cent of patients without hypertension had a similarly hyperactive sympathetic nervous system. This observation proved of value in two ways: First, in corroborating an extensive literature and, in particular, the findings of Kessel and Hyman,[25] concerning the existence of a sympathotonic group of individuals (which they termed "autonomic imbalance") characterized by the signs and symptoms of a hyperactive sympathetic nervous system, indistinguishable from exophthalmic goiter, in association with a normal basal metabolism. Twenty-nine of these 49 patients without hypertension were apparently of this group, and heretofore diagnosed "neurasthenia" and "hysteria." Second, from another point of view, the reactions of this type of individual were in reality an expression of a hypertonic sympathetic nervous system, and, therefore, not "functional" in the ordinary sense of the word.

The second generalization is in the nature of a corollary to the first. The value of any sign or symptom in the differential diagnosis of a disease lies not only in the frequency with which it occurs

in that disease, but in the infrequency with which it is found in other conditions. The ocular manifestations of sympathotonia are obviously of little significance in the differential diagnosis of exophthalmic goiter, judging from the frequency with which they are met in essential hypertension, chronic nephritis with hypertension and individuals of sympathotonic tendencies. This evidence of sympathotonia is of importance, however, because it is one of the few objective findings which indicate the actual state of tonicity and activity of the sympathetic nervous system from time to time and because it gives us some insight into the possibility of a more fundamental disturbance than has been suspected hitherto.

A third conclusion, which is obviously of significance, is the state of flux in the tonicity of the sympathetic nervous system which is suggested by our observations. It has been known for many years that exophthalmos may vary in intensity during the course of exophthalmic goiter with successive remissions and exacerbations. Ample evidence has been accumulated during our work to corroborate this statement, and to extend it to include the other eye signs of sympathotonia. The rhythmic increase and decrease in these signs of sympathetic nervous system hyperactivity may be at least another objective manifestation of the partial remissions and exacerbations which have been encountered in the nervous signs and symptoms of exophthalmic goiter, hypertension and sympathotonic individuals.

Study of the patients without hypertension but with sympathotonia reveals a fourth factor concerning the association of this condition with disease of the nervous system. Its occurrence in hysteria, epilepsy, primary familial muscular atrophy and post-encephalitic Parkinson's syndrome is of some interest, and the nature of its relation to these conditions certainly deserves further study.

Special emphasis should be placed on the relative frequency with which sympathotonia was detected in chronic arthritis. Tangible evidence has already been offered in the literature on the relation of the sympathetic nervous system to arthritis. Rowntree and Adson[26] (1929) have reported an unusual case in which sympathetic ganglionectomy and ramisectomy resulted in a remarkable remission in an advanced arthritis deformans of crippling proportions.

Finally, it seems of importance to recognize the relation which seems to exist between the mechanism of blood-pressure maintenance and the presence of sympathotonic tendencies. Hypotension was three times as frequent among patients without hypertension with eye signs as compared with those without eye signs. The frequency of eye signs in patients with hypertension has already been pointed out and seems unequivocal. Apparently the mechanism responsible for blood-pressure maintenance, whatever its fundamental nature, may be accompanied by sympathotonia and vary in intensity without reference to the tonicity of the latter.

Summary. 1. The history of exophthalmos and the eye signs with which it is often associated is considered from their anatomic, physiologic and clinical aspects.

2. The eye signs of sympathetic nervous system hyperactivity are specifically defined, and quotations are recorded from Stellwag, von Carion and Dalrymple in an effort to clear up the confusion in the literature concerning their eye signs.

3. Lidspasm, probably dependent upon sympathetic nervous system hyperactivity, has been described as a new eye sign and its significance is discussed.

4. The eye signs, hitherto considered classic of exophthalmic goiter, have been noted with surprising frequency in conditions other than Graves' syndrome (neurasthenia, chronic atrophic arthritis, hysteria, petit or grand mal, postencephalitic Parkinson's syndrome, pulmonary tuberculosis, duodenal ulcer, primary familial muscular atrophy, diabetes mellitus, paroxysmal auricular fibrillation and hypotension) and especially in essential hypertension.

5. This clinical study includes 494 patients, of which 258 consecutive cases had essential hypertension and 236 consecutive patients had a normal blood pressure or a hypotension.

6. The influence of position on the detection of lidlag and lidspasm is emphasized; methods for accentuating unilateral exophthalmos and examining for inequality of palpebral fissures are recorded.

7. The clinical data which are presented include: (*a*) The age frequency of essential hypertension and eye signs. (*b*) The relation of essential hypertension to the occurrence of various eye signs. (*c*) The remarkable manner in which eye signs appear and disappear on subsequent examinations. (*d*) The relative frequency of the individual eye signs.

8. The subjective and objective signs of a hyperactive sympathetic nervous system are indicated, and for convenience of reference are termed "sympathotonia."

9. Several broad generalizations naturally suggested themselves during the course of this investigation. (*a*) The widespread evidence of sympathotonia (exophthalmic goiter, essential hypertension, chronic nephritis with hypertension *et cetera*). (*b*) The ocular manifestations are of little value in the differential diagnosis of disease, but of great importance in indicating, objectively, the actual state of tonicity in the sympathetic nervous system. (*c*) The state of flux in the tonicity of the sympathetic nervous system with tendencies to remissions and exacerbations, as detected in the appearance and disappearance of the eye signs, is emphasized. (*d*) Attention is directed to the relation which seems to exist between the mechanism of blood-pressure maintenance and the presence of sympathotonia. The relative frequency of hypotension in patients with eye signs is pointed out and its significance is discussed.

There is in existence a syndrome clinically indistinguishable from exophthalmic goiter, with the exception of the fact that the

basal metabolism is normal. It is characterized by various significant combinations of the cardinal and accessory signs and symptoms of Graves' syndrome.

I am indebted to Dr. Henry A. Christian for the privilege of carrying out this clinical investigation and for his many valuable suggestions. My thanks are also due to Dr. George E. Shambaugh, Jr., for his aid in confirming and checking up on many of the eye signs.

BIBLIOGRAPHY.

1. Trousseau, A.: Du goitre exophthalmique ou maladie de Graves, Clinique médicale de l'hotel dieu de Paris, 1865, **2**, 458.

2. Filehne, W.: Zur Pathogenese der Basedow'schen Krankheit, Sitzungsberichte der physik.-med., Societät zu Erlangen, 1879, **2**, 177.

3. Müller, H.: Ueber einen glatten Muskel in der Augenhöhle des Menschen und der Saugethiere, Ztschr. f. wissensch. Zoöl., 1858, **9**, 541.

4. MacCallum, W. G., and Cornell, W. B.: The Mechanism of Exophthalmos, Med. News, 1904, **85**, 732.

5. Landström, J.: (1) Ueber Morbus Basedowii, Thesis, Stockholm, 1907; reviewed in J. Am. Med. Assn., 1909, **52**, 476. (2) Exophthalmic Goiter, According to Modern Views, Almänna svenka Läkaretidning, 1908, No. 48; abstracted in Ophthalmology, 1909, p. 675.

6. Bienfait, A.: Contribution á l'étude de la pathogenie du goitre exophthalmique, Bull. de l'Acad. roy. de méd. Belgique, 1890, **4**, 470.

7. Mendel, E.: Zur pathologischen Anatomie des Morbus Basedowii, Deutsch. med. Wchnschr., 1892, **18**, 89.

8. Bernard, C.: Des phénomènes oculopupillaires produits par la section du nerf sympathique cervical; ils sont independants des phénomènes vasculaires calorifiques de la tête, Compt. rend. de l'Acad. d. sc., 1862, **55**, 381.

9. Benard, H.: Contribution á l'étude du goitre exophthalmique, pathogenie, traitément, Thése de Paris, 1882.

10. Langley, J. N., and Sherrington, C. S.: On Pilomotor Nerves, J. Physiol., 1891, **12**, 278.

11. Jonnesco, T.: Physiologie du nerf sympathique cervical chez l'homme, Sect. physiol., XIII Cong. Internat. de Méd., Paris, 1900, p. 26.

12. Cannon, W. B., Binger, C. A. L., and Fitz, R.: Experimental Hyperthyroidism, Am. J. Physiol., 1915, **36**, 363.

13. Edmunds, W.: Observations and Experiments on the Pathology of Graves's Disease, Trans. Path. Soc., London, 1895, **46**, 224.

14. Jaboulay, M.: De la regénération du goitre extirpé dans la maladie de Basedow et la section du sympathique cervical dans cette maladie, Lyon méd., 1896, **81**, 389.

15. Jonnesco, T.: Traitément chirurgical du goitre exophthalmique, XI Cong. Français de chir., 1897, p. 284.

16. Balacescu: Die totale und bilaterale Resection des Sympathicus cervicalis beim Morbus Basedowii, Arch. f. klin. Chir., 1902, **67**, 59.

17. Kocher, A.: Ueber Morbus Basedowii, Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1902, **9**, 1.

18. Mayo, C. H.: The Surgical Treatment of Exophthalmos, J. Am. Med. Assn., 1914, **58**, 1147.

19. Von Graefe, A.: Ueber Basedow'sche Krankheit, Deutsch. Klin., Berlin, 1864, **16**, 158.

20. Kocher, T.: Zur Frühdiagnose der Basedow'schen Krankheit, Corr.-Bl. f. schweiz. Aerzte, 1910, **40**, 177.

21. Stellwag, von Carion, C.: Treatise on the Diseases of the Eye (translated from the fourth German edition), 1873, p. 521.

22. Dalrymple, J.: The Anatomy of the Human Eye, London, 1834, p. 266.

23. Sattler, R.: Exophthalmus, Arch. Ophthal., 1885, **14**, 190.

24. Barker, L. F., and Hanes, F. M.: Exophthalmos and Other Eye Signs in Chronic Nephritis, Trans. Assn. Am. Phys., 1909, **24**, 146.

25. Kessel, L., and Hyman, H. T.: II. The Clinical Manifestations of Disturbances of the Involuntary Nervous System (Autonomic Imbalance), Am. J. Med. Sci., 1923, **165**, 513.

26. Rowntree, L. G., and Adson, A. W.: Polyarthritis: Further Studies on the Effects of Sympathetic Ganglionectomy and Ramisectomy, J. Am. Med. Assn., 1929, **93**, 179.

REVIEWS.

THE PHYSIOLOGY OF THE VESTIBULAR APPARATUS. By MARIO CAMIS. Translated and Annotated by R. S. CREED, B.M., B.Ch., M.A. Pp. 310; 65 illustrations. New York: Oxford University Press, 1930. Price, $7.50.

THIS translation of Camis' monograph should prove extremely valuable to English readers who are unable to read the Italian original; and useful even to those familiar with Italian, since the translator has added many comments in which the statements of the original text are considered in the light of recent work by the Sherrington school. Written and translated by pupils of Sherrington it reviews the whole field of labyrinthine physiology, particularly in its relation to reflex activities. The historical aspects are fully treated; the functional disabilities resulting in animals from labyrinthine injuries are carefully described, including the somewhat neglected field of the effects of labyrinthine stimulation on the circulation, a field in which Camis himself has specialized.

The work of Magnus and de Kleyn is adequately covered as well as the interesting work of Schmaltz on the mode of stimulation.

Rotatory tests of labyrinthine function in man are treated shortly and without emphasis on their importance to aviation. While the view expressed that too much emphasis has been paid to the duration of nystagmus in estimating flying efficiency is sound, the importance of forced movements and wrong estimates of position following excessive labyrinthine stimulation in aviation has not been given here enough attention.

An excellent bibliography is included. H. B.

MANUAL OF PHYSIOLOGY. By H. WILLOUGHBY LYLE, M.D., B. S. (LOND.), F. R.C.S. (ENG.), and DAVID DE SOUZA, M.D., D.Sc. (LOND.), F.R.C.P. (LOND.). Pp. 820; 138 illustrations, 3d edition. New York: Oxford University Press, 1930. Price, $5.25.

THE compilation of a manual of physiology for medical students by a consulting surgeon and physician might appear to be an ideal arrangement, but in practice is a failure. This work may contain more physiological information than is possessed by the average

teacher of medicine but it provides a very inferior foundation for the medicine of the future. It is regrettable that the Oxford University Press has undertaken its publication, and that students' lack of judgment has resulted in its appearing in a third edition. While many sections of physiology are outlined with reasonable accuracy, the work can in no way be said to provide an adequate basis for the medicine of the future. For instance respiratory methods of measuring circulation rate receive no attention; the isolation of pitocin and vasopressin from pituitrin is not mentioned; the relation of the pituitary gland to the reproductive cycle is neglected; nystagmus of labyrinthine origin is assigned to interference between cerebellar and cerebral responses. This method of authorship is as successful as would be the writing of manuals of physics or medicine by professors of physiology.

H. B.

SURGICAL DIAGNOSIS, VOL. II. By 42 American Authors. Edited by EVARTS AMBROSE GRAHAM, A.B., M.D. Pp. 871; 834 illustrations. Philadelphia: W. B. Saunders Company, 1930. Price, $35.00, set of 3 volumes.

VOLUME II is a worthy follower of its fellow. The first 128 pages are given over to Gynecologic Diagnosis written by Curtis. This section is really a text in itself. Each portion is well illustrated and followed by a short bibliography.

The section on Diseases of the Face, Mouth and Jaws by Blair, and others, is overlapped to some extent by the following discussions on Diseases of the Neck by Forrester and Raine. Copher and Dick give a rather condensed section on the Thyroid and Parathyroid glands and a fairly complete bibliography.

The surgical Diseases of the Stomach and Duodenum are treated by Horsley and Horsley. They give an excellent section on the anatomy and physiology of these organs, and discuss the diagnosis as it can be made from the history, physical findings and laboratory examinations. The technique of the laboratory tests is briefly outlined. The place of the Roentgen-ray in the diagnosis of these diseases is well emphasized and illustrated by outline drawings.

Hertzler has written the section on the Diseases of the Peritoneum, and the chapter on Diseases of the Appendix, Small and Large Intestines is by Richardson. The discussions of the diagnosis and complications of appendicitis and of intestinal obstruction are excellent.

Pool and Stillman have followed their comprehensive monograph in the preparation of their section on the Spleen. The diagnosis of Hernia is given by Fisher and Cole. Full discussions are given

as to the etiology, signs and symptoms of the common and rarer forms. The last chapter on the Diagnosis of Abdominal Emergencies by Allen of necessity includes a discussion of many subjects already described. It should prove one of the most valuable chapters for quick reference as an aid in making a differential diagnosis.

MEDICINE MONOGRAPHS. VOLUME XVII. EPHEDRIN AND RELATED SUBSTANCES. By K. K. CHEN, and CARL F. SCHMIDT. Pp. 121. Baltimore: The Williams & Wilkins Company, 1930.

A MONOGRAPH giving the history of ephedrin with a critical review of the clinical and pharmacologic literature, most of which has accumulated since this drug was reintroduced into occidental medicine by the authors. The information contained is not yet available in textbooks of pharmacology or therapeutics. The comprehensive nature of this review (the bibliography contains over 500 titles), and its concise form make it important for those who wish to employ the drug, but who have no time to study the original articles bearing upon its action and usefulness. I. S.

A COMPILATION OF CULTURE MEDIA. By MAX LEVINE, PH.D., and H. W. SCHOENLEIN, M.S. Pp. 969. Baltimore: The Williams & Wilkins Company, 1930. Price, $15.00.

THE book is well printed and serviceably bound. It was "prepared at the request of the Society of American Bacteriologists, and financed by a grant from the Digestive Ferments Company."

The subject matter comprises directions for the preparation of 2543 different culture media, with their variants, which would comprise most, if not all, the recognized media in use for the cultivation of microörganisms.

The Reviewer has been unable to find any errors in the formulæ, nor omissions of useful media from the compilation.

The various media are classified according to their physical characters into seven groups, and by their clinical constituents into some forty or more sections.

There are four indices according to Medium Name, Constituents, Use, and Author, making it possible to find quickly any formula desired.

This work represents an enormous amount of painstaking labor, and should fill a useful place in every bacteriologic laboratory.

F. L.

HANDBOOK OF THE VACCINE TREATMENT OF CHRONIC RHEUMATIC DISEASES. By H. WARREN CROWE, D.M., B.CH. (OXON.), M.R.C.S., L.R.C.P. Pp. 52. New York: Oxford University Press, 1930. Price, 80 cents.

ANY book which claims to prove that the use of vaccines should make the prevention of chronic rheumatic diseases easy and allow every medical man to be in a position to treat his own rheumatic patients with a very fair measure of success is capable of doing much damage in the present state of our knowledge of this disease. If the only treatment in use at the Charterhouse Rheumatism Clinic is that by stock vaccines, it is natural that its director should be enthusiastic; perusal of his book, however, does not bring the conviction which he implies would be afforded by an ocular demonstration at his Clinic. We object to his basic but unproved and frequently opposed hypothesis that all rheumatic diseases are bacterial in origin, we are suspicious of views that are at times based on evidence that might be otherwise construed and often are expressed in incautiously enthusiastic terms, and we regret the almost complete absence, even in a book of this small size, of objective data to support rather sweeping claims. E. K.

A TEXT-BOOK ON ORTHOPEDIC SURGERY. By WILLIS C. CAMPBELL, M.D., F.A.C.S. Pp. 705; 507 illustrations. Philadelphia: W. B. Saunders Company, 1930. Price, $8.50.

THOUGH not exhaustive Campbell's text-book is extremely well done. The arrangement of material is good and the relative space allotted to the various subjects is well proportioned.

That the treatment of fractures should be the work of the orthopedic surgeon is now accepted but it seems improper and almost futile to attempt to cover so vast a subject in the limited space of a single volume devoted to orthopedics in general.

The bibliographies appended to the various subchapters, are not extensive but for the most part well selected. The volume is strongly recommended as a text-book for students. G. W.

TEXT-BOOK OF HISTOLOGY. By ALEXANDER A. MAXIMOW, Completed and edited by WILLIAM BLOOM. Pp. 833; 604 illustrations. Philadelphia: W. B. Saunders Company, 1930. Price, $9.00.

FOR some years before his death in 1928 Professor Maximow was engaged in the preparation of a text-book of histology. To his colleague Professor Bloom has fallen the task of completing the

work, which has just appeared. Professor Bloom has had the coöperation of the staff of the anatomical department of the University of Chicago, and the result is an important addition to American textbooks of histology. To all students of blood-formation and connective tissue cells Professor Maximow's brilliant researches are well known, and it is the parts of the book dealing with these topics that are most characteristic. In the chapters on blood, connective tissue proper, blood-forming and blood-destroying tissues, and spleen the illustrations are mostly original. They either appear now for the first time, or they are taken from Maximow's previous publications. In other chapters the figures are mostly taken from the works of others, some from special monographs, also many from the textbook of Schaffer. The latter is the case notably in the chapters on the special senses. The tissues of the nervous system are treated in eleven short chapters, chiefly by Professor Herrick. There is no description of cerebral or cerebellar cortex, or other regions of the brain. Under the heading of histophysiologic remarks, there is constant reference to function, though, of course, the description of structure is the main consideration. In practically every chapter there is a short account of the histogenesis of the tissue or organ being described. No technique is included, but a limited number of references is usually given at the end of a chapter. The book will be of interest to physiologists and pathologists as well as to anatomists. W. A.

APHASIA IN CHILDREN. By ALEX W. G. EWING, M.A., PH.D., with an introduction by E. D. ADRIAN, M.D., F.R.C.P., F.R.S. Pp. 152. New York: Oxford University Press, 1930. Price, $3.50.

EWING found that of 10 cases of "aphasia" in childhood, manifesting either absence of or gross defects in speech and language, 6 showed a marked, binaural lack of hearing for ascending orders of frequency in sound above 256 v.d. This deficiency was associated with normal or relatively normal hearing for sounds of frequency below 256 v.d. He showed that this lack of auditory acuity for the higher frequencies of sound had abolished the characteristic differences of the sounds of speech for these patients. He reached the very interesting conclusion that these cases showed no trace of the defects characterizing aphasia, and that in their speech and language development these cases passed through the same stages as the normal child. The tests made in Ewing's work were all done by the audiometer and were carefully controlled. The results indicate that the defect in these high-frequency deaf children may be in the cochlea, along the auditory path, or possibly even to late

myelination of the nerve fibers associated with hearing. Ewing prefers to use the term linguistic retardation for the type of case which he describes, rather than congenital aphasia. It is possible to educate these children to recognize sounds of the higher vibration frequencies.

The monograph is an interesting contribution. Its value is twofold: the discovery of a type of case hitherto looked upon as an incurable aphasia, and the working out of a systematic method of testing hearing through its various ranges. The latter has led to the discovery noted, and should be carried out systematically in adult cases of aphasia as in the cases reported by Ewing. The book is a real contribution and can be recommended highly to otologists, neurologists, and all those interested in speech. B. A.

PERNICIOUS ANEMIA. By LEYBOURNE STANLEY PATRICK DAVIDSON, B.A. (CAMB.), M.D., F.R.C.P.E., and GEORGE LOVELL GULLAND, C.M.G., LL.D., M.D., F.R.C.P.E. Pp. 203; 30 illustrations. St. Louis: The C. V. Mosby Company, 1930. Price, $8.50.

A CRITICAL summary of the various aspects of the pernicious anemia problem is of especial interest today, when so many new and important observations have been made as to its manifestations and efficacious treatment, without as yet solving the problem of its real nature. The authors have very ably accomplished their task of presenting such a review, based on a wise selection from the rather plethoric literature on the subject; and also have not hesitated to express their own views derived from a considerable experimental and clinical experience with the disease.

The opening historical chapter presents four periods: (1) Addison's and the British clinical observations; (2) Biermer's and the German widening and popularizing of the concept; (3) the contributions of Hunter, Ehrlich and others to pathologic and hematologic knowledge of the disease; (4) the past decade with its increased knowledge of blood formation and blood destruction and especially the invaluable discovery of liver as a therapeutic agent.

Following a good description of the pathologic anatomy of the disease comes a lengthy discussion of bacteriology, including the reproduction in full of a paper by one of the authors. As the results of this paper were wholly of a negative character, the general conclusions (p. 63) and the original reference would seem to have been sufficient.

In the discussion of etiology (p. 102 *et seq.*), the German view, that the disease is primary in the bone marrow as a disorder of blood formation, is preferred by the authors to Hunter's (and the

English) view that the primary site is in the gastrointestinal tract with a hypothetical hemolytic agent. The Reviewer has pointed out elsewhere that the therapeutically active liver substance of Minot (and now the gastric extracts of Castle) point to a deficiency nearer the primary source of the trouble than are the phenomena either of excessive blood destruction or abnormal blood formation. That the authors themselves recognize the importance of these etiological relationships is shown by their thorough discussion of the unknown specific factor necessary for normal blood formation (p. 110 *et seq.*).

Adequate further chapters on symptoms, blood and metabolic changes, diagnosis, prognosis and treatment and an appendix on dietotherapy complete the presentation, which we consider as the best review of a subject about which much has recently been written.

E. K.

BOOKS RECEIVED.

NEW BOOKS.

*Selected Readings in the History of Physiology.** Edited by JOHN FARQUHAR FULTON, M.D. Pp. 317; 61 illustrations. Springfield, Ill.: Charles C. Thomas, 1930. Price, $5.00.

*Stalkers of Pestilence.** By WADE W. OLIVER, M.D. Introduction by THEOBALD SMITH, M.D., PH.D. Pp. 251; 23 illustrations. New York: Paul B. Hoeber, Inc., 1930. Price, $3.00.

*History of Haitian Medicine.** By ROBERT P. PARSONS. Foreword by EDWARD R. STITT. Pp. 196; 21 illustrations and map of Haiti. New York: Paul B. Hoeber, Inc., 1930. Price, $2.25.

*The Candiru.** By EUGENE WILLIS GUDGER, PH.D., with a Foreword by ALFRED SCOTT WARTHIN, PH.D., M.D., LL.D. Pp. 120; 18 illustrations. New York: Paul B. Hoeber, Inc. ,1930. Price, $1.50.

*Histology for Medical Students.** By H. HARTRIDGE, M.A., M.D., Sc.D., M.R.C.P., F.R.S., and F. HAYNES, M.A. Pp. 369; 512 illustrations. New York: Oxford University Press, 1930.

*Laboratory Medicine.** By DANIEL NICHOLSON, M.D. Pp. 433; 108 illustrations. Philadelphia: Lea & Febiger, 1930. Price, $6.00.

*An Introduction to Malariology.** By MARK F. BOYD. Pp. 437; 82 illustrations. Cambridge, Mass.: Harvard University Press, 1930. Price, $5.00.

*A Text-book of Pathology.** By E. T. BELL, M.D. Pp. 627; 316 illustrations. Philadelphia: Lea & Febiger, 1930. Price, $8.00.

*Practical Midwifery for Nurses.** By BETHEL SOLOMONS, M.D., F.R.C.P.I., M.R.I.A. Pp. 354; 136 illustrations. New York: Oxford University Press, 1930. Price, $2.75.

*Outline in Obstetrics for Nurses.** By F. W. RICE, M.D. Pp. 228; 56 illustrations. St. Louis: The C. V. Mosby Company, 1930. Price, $2.00.

*La Rate, Organe Réservoir.** By LEON BINET. Pp. 116; 17 illustrations. Paris: Masson et Cie, 1930. Price, 20 Fr.

* Reviews of titles followed by an asterisk will appear in a later number.

The Edwin Smith Surgical Papyrus being Vols. III and IV of the University of Chicago Oriental Institute Publications, Vol. I, Hieroglyphic Transliteration Translation and Commentary. Pp. 596; 8 plates. *Vol. II, Facsimile, Plates and Line for Line Hieroglyphic Transliteration.* Pp. 13; 22 plates.* Edited by JAMES HENRY BREASTED. Chicago: The University of Chicago Press, 1930. Price, $20.00.

Index of Transactions of the American Otological Society, Vols. I to XVIII. Years 1872 to 1928, inclusive. Pp. 148. Published by the Society, 1929.

Het Kruis der Leprozen. By DR. DENIS MULDER. Pp. 135; 30 illustrations. Bandoeng, Java: Maks & vander Klits, 1930. Price, F. 1.50.

A description of 30 years' fight against leprosy in the Dutch East Indies.

Guy's Hospital Reports, Vol. 80, No. 3—July, 1930. Edited by ARTHUR F. HURST, M.D. Pp. 378; illustrated. London: The Lancet, Ltd., 1930. Price, 12/6 net.

Standards for Maternity Care. Prepared by THE COMMITTEE ON MATERNITY CARE OF THE CHILDREN'S WELFARE FEDERATION and A COMMITTEE APPOINTED BY THE NEW YORK OBSTETRICAL SOCIETY. Pp. 31. New York: The Children's Welfare Federation, 1930.

These Standards were published in part in the American Journal of Obstetrics and Gynecology in the issue of July, 1930. Copies of the Standards may be secured from the Children's Welfare Federation, 244 Madison Ave., New York City.

Medical Care for 15,000 *Workers and Their Families.* With reports on certain phases of the organization by NELLIS B. FOSTER, M.D., RANSOM S. HOOKER, M.D., and MICHAEL M. DAVIS, PH.D. Pp. 23; 2 illustrations. Washington, D. C.: The Committee on the Costs of Medical Care, 1930.

This is the fifth publication by this Committee on a topic of great practical importance to the profession.

The Medical Clinics of North America, Vol. XIV, No. 2 (New York Number, September, 1930). Pp. 273; 73 illustrations. Philadelphia: W. B. Saunders Company, 1930.

NEW EDITIONS.

*Intestinal Tuberculosis—Diagnosis and Treatment.** By LAWRASON BROWN, M.D., and HOMER L. SAMPSON. Pp. 376; 124 illustrations. Second Edition. Philadelphia: Lea & Febiger, 1930. Price, $4.75.

Elementary Zoölogy for Medical Students. By L. A. BORRADAILE, SC.D. Pp. 397; 251 illustrations. Second edition. New York: Oxford University Press, 1930.

An abbreviation of the author's "Manual of Zoölogy," containing rather elementary descriptions of a few type animals such as the frog, a few protozoa, and worms, crayfish, cockroach, fly and mosquito, dogfish and rabbit.

Handbook of Anatomy. By JAMES K. YOUNG, M.D., F.A.C.S. Revised by GEORGE W. MILLER, M.D., F.A.C.S. Pp. 460; 154 illustrations. Seventh edition. Philadelphia: F. A. Davis Company, 1930. Price, $3.75.

Minor Surgery and Bandaging. By GWYNNE WILLIAMS, M.S., F.R.C.S. Pp. 445; 262 illustrations. Twentieth edition. Philadelphia: F. A. Davis Company, 1930. Price, $3.50.

A Text-book of Histology. By HARVEY ERNEST JORDAN, A.M., PH.D. Pp. 857; 596 illustrations. Fifth edition. New York: D. Appleton & Co., 1930.

In this edition, several figures have been improved by the substitution of new drawings, and minor changes have been made in the text on blood and endocrine tissues.

* Reviews of titles followed by an asterisk will appear in a later number.

PROGRESS

OF

MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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Sprue Treated With Liver.—WILKERSON (*South. Med. J.*, 1930, **13**, 947) reports upon an individual who had sprue who was given liver as a therapeutic measure to control the disease. When this patient was first observed he was thin, emaciated and had a pronounced anemia, together with the stools that are characteristic of sprue. He was given an appropriate diet, to which was added liver and liver extract. In the first month, bowel movements were normal and the red count had increased pronouncedly. In three months he was to all intents and purposes well and the blood count had increased 2,600,000 red cells, or to normal figures. In discussing the pathogenesis of sprue, he suggests that there must be a similar deficiency in pernicious anemia and sprue—a deficiency which is made up by the liver. In one case it might arise because of the inability of the patient to eat; in the other instance because of the inadequate gastric digestion of protein.

Bacteriology of the Blood in Chronic Infectious Arthritis.—First Rosenow and then Cecil and his coworkers advanced the hypothesis, and attempted to substantiate it by experimental methods, that chronic arthritis is a result of infection and this infection is due to a definite bacterial agent which may be obtained from blood culture of individuals suffering from this type of disease. Cecil was able to get 61.5 per cent positive cultures of a Gram-positive micrococcus with the morphologic characteristic of streptococci. This organism injected into animals produced arthritis. MARGOLIS and DORSEY (*J. Infect. Dis.*, 1930, **46**, 442) used a technique for cultures of the blood from arthritics that was of their own devising; they employed Cecil's modification of Clawson's method; they followed out Rosenow's technique and in a few cases cultured the blood in placenta broth. Ninety-two patients were observed, 89 of whom had chronic arthritis and 3 of whom had acute or subacute

rheumatic fever. Of the 89 patients, 49 had two parallel blood cultures by two different methods and 10 by three methods and the remaining 33 patients by one of the four methods. In only 5 patients were the cultures repeated. From 162 blood cultures streptococci were isolated in 4 instances by their own technique. Of the 68 blood cultures made by the method of Cecil, 3 cultures developed green-producing streptococci and 2 diphtheroids. The remaining 63 were sterile. Following the method of Rosenow in 11 instances, all the cultures were negative. One hundred and fifty-one cultures were sterile; 11 were positive, 6 with a green-producing streptococci, 3 with indefinite streptococci and 2 with diphtheroids. Their results are not comparable to those of Cecil and his group. Only a very small percentage of the cultures were positive, whereas with Cecil's there were well over 50 per cent positive. The final conclusion of these two authors that the occurrence of the organisms in the blood as well as in the joints of patients with arthritis suggests that these bacteria are of etiologic significance in this disease hardly seems justifiable in view of the bacteriologic studies that are reported in this paper.

Seasonal Variation in Efficiency of New Orleans Sunshine and Skyshine in Preventing and Curing Rickets in Rats.—MAYERSON and LAURENS (*Proc. Soc. Exper. Biol. and Med.*, 1930, **27**, 1070) report upon a large series of rats fed the Steenbock and Black rickets-producing diet, who were divided into groups, when weaned, and exposed to sunshine and skyskine for varying lengths of time. The controls showed florid rickets in five weeks. The test animals, on the contrary, when exposed to sunshine for three minutes did not develop the disease. During the winter months, an average daily exposure of ten minutes protected the animals, but five minutes did not. During the spring months, April and May, an average daily exposure of six minutes protected them. Exposure to skyshine necessarily was considerably longer. For example, during July exposure for twenty-four minutes was borderline, whereas forty-eight minutes afforded complete protection. These observations are of considerable interest. The confirm definitely that sunshine and skyshine are able to protect the experimental animal against rickets and they show that extremely short exposure is necessary in order to bring this about.

Frequent Chest Colds. Variability in Their Occurrence and the Bacteriology in Those Very Susceptible to This Type of Cold.—WALKER and ADKINSON (*Arch. Inter. Med.*, 1930, **46**, 1) write that their paper deals with individuals who customarily have three or more chest colds a year over a number of years and who were studied at the time of the cold. They present a careful bacteriologic study of the flora isolated from the sputum of these patients. They show as a result of their study that there is considerable variability in the occurrence of chest colds in those who are susceptible, an individual characteristic not dependent on extraneous conditions. Many varieties of streptococci are found in sputum and this is the organism most frequently present. They hold because of this fact and because vaccines containing the most prevalent varieties of streptococci seem to prevent or benefit a cold in the chest that it is reasonable to assume that streptococci play a part in the causation of this common disorder.

SURGERY

UNDER THE CHARGE OF

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The Structure and Function of Articular Synovial Membranes.—SIGURDSON (*J. Bone and Joint Surg.*, 1930, **12**, 603) state that the inner surface of articular capsules is not formed by a distinct membrane but by connective tissue modified as the synovial surface is reached. The cells here are more closely packed and the nuclei exhibit peculiar staining characteristics, but that does not seem to justify the use of the term membrane. The superficial synovial cells are not uniform in size or shape, some being quite small and round, while others are large with branching processes. Synovial villi vary greatly in size and shape and are composed of connective tissue resembling the part of the capsule from which they arise. The presence of stomata in articular capsules is not confirmed.

Changes in the Spinal Fluid Following Injection for Spinal Anesthesia.—IOSON, LEDEREN and STEINER (*Surg., Gynec. and Obst.*, 1930, **51**, 76) say the pleocytosis (cell increase) would seem to indicate a certain amount of irritation of the serous lining of the subarachnoid space, but whether it was due to a general irritation of the whole extent of the dura or only of the immediate neighborhood of the puncture, it is impossible to say from these observations on the human subject. The increase in sugar, together with the increase in lymphocytes in the spinal fluid might be interpreted in the nature of mild encephalitis. However the absence of sequelæ in more than half of the cases studied, as well as the rapid disappearance and the mild character of symptoms present after spinal anesthesia would argue against this. Further studies are being made in which simultaneous blood and spinal fluid sugar determinations are being done, before and after, novcain injection, in order to observe if any relationship exists between the sugar content of the blood and spinal fluid under these conditions.

An Anatomical Study of Subdural Hemorrhage.—CHASE (*Surg., Gynec. and Obst.*, 1930, **52**, 31) says that subdural hemorrhage is the important intracranial lesion in most cases of birth trauma. There is nothing to indicate that intradural hemorrhage or tentorial splits *per se* are of noteworthy clinical significance. The subdural hemorrhage is largely supratentorial and often bilateral. It is usually due to a stretching and rupturing of the small tributaries of the great cerebral vein near its junction with the straight sinus. Tentorial splits are relatively more numberous in the premature than in the full-term infant, partly because of the greater immaturity of fibers of the dural septa in prematurity. The causes of prolonged and difficult labor may be equally as important in these intracranial lesions as the operative interference. Signs of asphyxiation were constant but definite signs of intracranial irritation were recorded in only a small minority of cases.

THERAPEUTICS

UNDER THE CHARGE OF

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Clinical Investigations on the Comparative Effectiveness of Various Hypnotics by Oral and Rectal Administration.—FRIEDMANN (*Deutsch. med. Wchnschr.*, 1930, **56**, 867) reports the results of a careful comparative investigation of a variety of hypnotics administered to adult males weighing between 60 and 70 kg. He attempts to determine an effective dose which will induce sleep during the day, as well as attempting to determine the rapidity and duration of action of the individual drugs and of certain combinations. Two grams of abasin proved highly sedative but not very effective as a hypnotic. It failed to produce sleep in 8 out of 20 patients, once following oral administration and 7 times following rectal. It required more than two and a half hours to induce sleep and the sleep lasted less than four hours. It is much less effective by rectum than orally. Much the same results are obtained from a combination of 0.3 gm. of bromural with an equal quantity of pyramidon, except that there is no essential difference in effectiveness between the oral and rectal administration of this combination. A single dose of 2 gm. of adalin is much more effective as an hypnotic. This failed to produce sleep in only 6 cases. The resulting sleep lasts up to seven hours and comes on within thirty minutes to several hours after administration. It is about twice as effective orally as rectally. Amylene hydrate proves to be an hypnotic of great value and is more effective by rectal than oral administration. A dose of 3 gm. produced effective sleep for four to eight hours in all but 2 of 16 patients, and sleep developed within one and a half to three and a half hours following administration. Potassium bromide behaves essentially as does abasin. Hydrated chloral proved to be the most satisfactory of all hypnotics studied. It is necessary, however, to watch its administration in order to avoid cumulative effects, especially chronic cardiac intoxication. It is equally effective orally and by rectum. A combination of 0.3 gm. of luminal with 5 gm. of urethane, theoretically, should be almost as effective as hydrated chloral, but clinical observation shows it to be chiefly sedative rather than hypnotic. Only 9 out of 25 patients obtained satisfactory sleep. This combination is best given rectally. Sodium barbital, in doses of 1 gm., is particularly effective as a hypnotic. In 21 out of 25 cases it produced sleep in from fifteen minutes to two hours. Since the gastric juice splits barbital sodium into barbital and sodium chlorid, it is better for oral administration to employ barbital and for rectal, barbital sodium. Noctal,

either in doses of 0.4 gm. orally in tablet form or rectally in suppositories, is a fairly effective hypnotic, but its action is not very trustworthy. A new preparation, novonal, is also only fairly effective. Sedormid, in doses of 2 gm., produces satisfactory sleep when given orally, but is merely sedative when administered by rectum. It should be a highly useful agent, but its cost is prohibitive. A combination of 0.5 gm. of barbital with 2 gm. of hydrated chloral, instead of proving more effective than each of these agents singly, proved distinctly less effective. Where prolonged continued sleep is required the administration every night of 2 gm. of sulphonal with 2 gm. of trional is effective, but sleep in the daytime is better secured by the administration of 1 mg. of scopolamin combined with 10 gm. of paraldehyd, the dose being varied to suit the patient. The most effective prolonged sleep, however, is to be secured from 1 mg. of scopolamin, 10 mg. of morphin and 0.4 gm. of sodium luminal administered subcutaneously. The resulting sleep is as effective as that obtained from avertin and is much more readily controlled. Avertin narcosis, however, is effective where prolonged sleep is desired, and it may later be replaced by noctal.

The Inactivation of Insulin.—An attempt has been made by SCHMIDT (*Klin. Wchnschr.*, 1930, **9**, 1021) to determine where and how insulin is rendered inactive in the body. He reports in the present article the results of a variety of experiments. In the first group it is shown that insulin may be rendered inactive by incubation with finely-ground animal tissues. One gram of fresh muscle produces slight inactivation of 10 units of insulin; the same amount of ground spleen almost completely inactivates 10 units; kidney inactivates more than 10 units but less than 25 per gram, while liver destroys more than 25 units but less than 50. By suitable filtration of fresh, finely-ground tissue to remove the cells, a tissue juice is obtained in the form of glycerin extract. These extracts are found to be significantly weaker than the minced tissues but, like the former, they are capable of inactivating insulin when incubated with it.

Again, the extract of liver is found to be the most potent. Heating of these fluid extracts to 100° C. completely destroys their power of inactivation, indicating that it is due to some ferment. Acidification of the extracts also destroys their potency. Second in its capacity to destroy insulin is kidney extract, while extracts of lung and spleen are feeble and that of muscle is inactive. Although the precise chemical composition of insulin is not known, evidence points to its belonging to the protein group of substances as it is destroyed by the alkalies, pepsin and trypsin. From these facts the author reasons that the tissue ferments responsible for its destruction in his experiments belong to the group of proteolytic ferments known to be present in almost all tissues of the body. The injection of insulin into animals is followed by more rapid action when given intravenously than subcutaneously, but the toxic effects of insulin are more marked following the subcutaneous than the intravenous injection, indicating that, following intravenous injection, a large proportion of the circulating insulin is rapidly destroyed, probably in the liver, and others have shown that a dose of insulin is much more slowly destroyed in an animal the liver of which has been removed from the circulation than in an intact animal. In

closing, the author suggests that possibly in those cases of diabetes which it is difficult to control with even very large doses of insulin, there may be present an excessive amount of proteolytic ferment in the liver or other tissues which leads to very rapid destruction of the drug.

The Influence of Extract of the Anterior Lobe of the Pituitary in a Case of Dystrophia Adiposogenitalis.—It is a well-known fact that in dystrophia adiposogenitalis the metabolism is so altered that the usual specific dynamic action of protein is greatly reduced below that for normal individuals, along with other manifestations of the disease. J. T. PETERS (*Klin. Wchnschr.*, 1930, **9**, 1219) gives in detail the results of the administration of anterior lobe extract hypophysis in a typical case occurring in a nineteen-year-old girl. Prior to the administration of this extract all forms of treatment were tried without avail. Promptly after the beginning of anterior lobe administration the patient's headache disappeared; muscular strength improved along with marked improvement in her gait. Menstruation which had not previously appeared also began. With these symptomatic evidences of improvement there was conclusive objective evidence in the rapid rise in the specific dynamic action of protein, as determined by metabolic tests. This rise reached the fully normal level. The author states that this is, so far as he could discover, the first instance of such a remarkable recovery and the first in which the relation between the specific dynamic action, the function of hypophysis and ovarian function in man have been demonstrated as definitely as these relationships have been in animals.

PEDIATRICS

UNDER THE CHARGE OF

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Poliomyelitis.—CAMPBELL and MIRSKY (*Arch. Ped.*, 1930, **47**, 543) states that this disease has been known from the earliest times. During the twentieth century it attained epidemic proportions. The disease is caused by an invisible filter-passing virus which in the blood stream of recovered cases remains inert as it is held in combination by an immune body. This combination does not actually destroy the virus, which has extraordinary power to resist adverse living conditions. By the means of cataphoresis the virus can be dissociated from the immune body. Most cases of the disease are subclinical and escape diagnosis. The infection usually takes place during the early years. Second attacks have not been reported. General systemic invasion usually precedes but may occur coincidently with the involvement of the nervous system. Poliomyelitis may be simulated clinically and pathologically by other diseases. The importance of diagnosis in the preparalytic stage is outstanding because the intramuscular injection of convalescent serum at this stage seems to prevent the development of paralysis.

Differential White Count in Infancy.—SMITH (*Am. J. Dis. Child.*, 1930, **40**, 505) studied the differential white counts of 37 normal and sick infants from a supravital preparation and from fixed smears. In forty-three of forty-eight comparative smears the percentage of polymorphonuclear leukocytes was higher, and that of lymphocytes was lower in the living preparation than in the fixed film. The average of twenty-four counts from the group of normal infants showed the percentage of polymorphonuclear neutrophils to be 8.6 per cent higher in the supravital than in the fixed cover-slip smear and almost 12 per cent higher than in the slide. The lymphocytes, on the other hand, ran 14 per cent and 11 per cent higher in the fixed smears of the slide and cover slip, respectively, than the corresponding cells of the supravital preparation. The principal reasons for this discrepancy are unequal distribution of the cells and failure to identify and include all fragmented polymorphonuclear leukocytes in the differential count of the fixed smear. With the supravital technique the spread of cells is more even, trauma is reduced, and both motile and dying cells may be more readily identified. The lymphocytes have always been regarded as the predominant cell in the blood of the infant. This observation has heretofore been based on differential counts using the fixed smear with some form of the Romanowski stain. While counts made from the supravital film confirm the preponderance of lymphocytes over polymorphonuclear leukocytes, it is often by no means as marked as indicated in the fixed smear. The differential count from the fixed smear may unduly exaggerate the lymphocytic percentage and convey the erroneous impression of a blood dyscrasia. In pyogenic infections, especially when associated with a leukocytosis, the differential count from the fixed smears gives at times a much lower polymorphonuclear and a higher lymphocytic percentage than expected. That this discrepancy is often due to an increased fragility of the polymorphonuclear leukocytes is evident from comparative supravital studies. In a routine differential count from the fixed smear, particularly when it is employed as an index of the patient's resistance, the extent of white-cell damage observed on the slide should be noted. If fragmented cells have been included in determining the individual cell percentages, mention of this fact also should be made.

The Relation of Infection of the Ear and Intestinal Tract in Infants.—WISHART (*J. Am. Med. Assn.*, 1930, **95**, 1084) reminds us that many authors believe that infection in the mastoid antrum is the cause of acute intestinal intoxication in infants. Study of the disease has been pursued for a period of five years, during the last two years of which a large body of observers have coöperated. The onset of the disease is rarely characterized by a cold. The great majority of infants were without any clinical evidence of upper respiratory infections at the time that they became toxic. Many infants remained without any clinical evidence of ear infection throughout the entire course of the illness. All accumulations or infections found in the mastoid antrums of infants at autopsy were antemortem in origin. Both ear drums of many showed abnormality immediately preceding death. This change

is an antemortem phenomenon due to forcible ejection up to the Eustachian tubes. When mastoid infection exists it is the result and not the cause of the child's lowered condition. Mastoid antrum puncture for diagnosis of latent mastoiditis is not without its dangers and is not to be recommended. Bilateral mastoid operations as a cure for the disease in this series was a failure. It is recommended that operation be postponed as long as possible. The autopsies of the 2 intensively studied series of cases of acute intestinal intoxication showed that mastoid infection was not common. There was no correspondence between the bacteriology of the infection in the upper respiratory tract and that in the intestinal tract. The author is attempting to gather evidence that will prove that the disease is of intestinal origin.

Menstrual Disorders in Adolescent Girls.—LAWRENCE (*J. Am. Med. Assn.*, 1930, **95**, 1148) states that the occurrence of delayed menses or abnormal menstrual rhythm or flow in adolescent girls is indicative of subnormal development of the reproductive glands, which is likely to result in diminished fertility during adult life. It is more often due to systemic functional disturbances than to pelvic disease, and of these disturbances insufficiency of the anterior pituitary hormone is the commonest. Spontaneous compensation of such conditions does occur, and treatment is not indicated by slight delay in establishing normal menstruation, but if that function has not become normal by the sixteenth year, the attitude of optimistic expectancy must be abandoned. In the great majority of these adolescent patients, the symptoms are not due to primary ovarian insufficiency, but to some endocrine or nonendocrine systemic condition that renders the potentially normal ovary inert. The commonest of these conditions are focal infection, insufficient protein in the diet, and the insufficiency of the anterior pituitary hormone. In this series the oral administration of anterior lobe pituitary substance, in adequate dosage, gave encouraging results in patients in whom the existence of such a pituitary insufficiency was demonstrated.

The Leukocytes in the Blood of Children.—ERLICH (*Rev. Fran. de Ped.*, 1930, **6**, 475) studied the blood of about 500 children, ranging in age from one day to fourteen years. He was endeavoring to determine the pathologic modifications of the leukocytes in various diseases. Leukocytosis, deviation to the left and toxic changes in the cells were found to be more or less important symptoms in the diagnosis of septicemia, erysipelas, pneumonia, ulcerative stomatitis, suppurative appendicitis, tuberculous meningitis, Heine-Medin disease, nontuberculous meningitis, typhoid, bacillary dysentery, acute colitis, scarlatina, measles, nontuberculous bronchial pneumonia, congenital and visceral syphilis, von Jaksch's anemia, pseudoleukemia, lymphosarcoma, granulomatosis, and severe alimentary intoxication. On the other hand no modifications of any note were found in tuberculous pleurisy and peritonitis, and various forms of anemia.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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Simple Method of Tubal Sterilization.—Many methods of sterilizing the female have been described and it has been said that every type of operation on the tubes has at some time failed of its purpose. The method which is described by BISHOP and NELMS (*N. Y. State J. Med.*, 1930, **30**, 214) is one which they have used in 100 cases without having pregnancy follow in a single one, so that they feel that the technique is "safe, simple and secure." The operation consists of ligating a loop of the middle loose portion of the tube with *absorbable* suture material and resecting it. They use a double strand of No. 1 chromic catgut. No absorption occurs until the danger of bleeding has passed and when the ligature has been absorbed, the two cut ends of the tube draw apart, as they have noted in subsequent laparotomies. During this period the plastic exudate of the peritoneum has been thrown out and become organized and thus Nature throws a barrier of new peritoneum which becomes a permanent cover with no chance of fistula formation between the cut ends of the tube. They emphasize that they do *not* crush the tube for the crushed tissue may open a way for fistula formation and for the same reason nonabsorbable ligature material is not used, as it might slough through and leave a fistula which could reëstablish the tubal lumen.

Vesicocervical Fistula.—The repair of a fistulous communication between the bladder and the cervix is often a very tedious and difficult operation on account of the depth of the lesion with the coincident poor exposure. In cases of this type GOTTLIEB (*Zentral. f. Gynec.*, 1930, **54**, 1090) has found that the treatment of the fistula by means of electrocoagulation gives very satisfactory results. While he first tried this method in cases of vesicocervical fistula it can also be used in cases of vesicovaginal fistula when the communication is of small caliber. The method is technically easy, safe, and causes so little pain that no anesthesia is necessary as a rule. Of course many of these small fistulas heal spontaneously but he believes that this method should be tried in cases where healing has not occurred after a period of six weeks. The method which he uses consists of the introduction of a cystoscope into the bladder in order to locate the vesical end of the opening, after which an electrode is passed through the cystoscope and into the fistulous opening as far as it will go. The fistulous tract is then coagulated in its entirety by slowly withdrawing the electrode with the current on. In this manner the epithelial lining of the fistula is destroyed and fresh granulations gradually fill in the tract, thus closing the artificial opening with consequent cure.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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Sudden Allergic Reactions Localized in the Antrum.—Stating that the appearance of polypi, of diffuse edema, and of similar filling defects commonly noted in radiographs of antrum, has long been regarded as a result of chronic inflammation, and in many quarters is considered sufficient evidence of hyperplasia to justify more or less radical operative interference, PROETZ (*Ann. Otol., Rhinol. and Laryngol.*, 1930, **39**, 87) recounts 3 cases, from the study of which he concludes that the antral mucosa may increase to ten or more times its normal thickness during an allergic attack; a single sinus may be involved; the obliteration of the antrum as demonstrated by roentgenologic examination, is not necessarily hyperplasia, and allergy should be excluded before operation is undertaken; and that a mineral oil is the logical diluent for radiopaques to be used in allergic individuals.

Otosclerosis: A Metabolic Disorder.—Regarding otosclerosis as a metabolic disease analogous to osteomalacia and rickets in that a state of hypoparathyroidism obtains in all of them, MIRVISH (*J. Laryngol. and Otol.*, 1930, **45**, 449) administered parathormone hypodermatically to three "otosclerotics." In one case the progress of the deafness was arrested and in the other 2 it was improved. The author states that rickets can be produced in two ways: either by a deprivation of vitamin D or by an excess of "calcovarin"—a substance he says he found in extracts of ovary, suprarenal cortex and "probably testis"—which reduces the blood calcium in characteristic manner both in rabbits and man. He also states that he encountered a similar rachitogenic factor in certain cereals, especially oatmeal.

The Rôle of Nasal Accessory Sinus Membrane in Systemic Infections and Toxemias.—LAWSON (*Ann. Otol., Rhinol. and Laryngol.*, 1930, **39**, 159) believes that in sinuitis clinical manifestations are due usually to the absorption of toxins, although in some instances the sinus may act as a true focus of infection. He is in doubt as to whether the toxic material is absorbed from the sinus mucosa or from more of highly absorptive tissues which receive it. Uncomplicated sinuitis rarely produces severe constitutional symptoms. Low-grade, prolonged toxemia from sinuses may cause visceral degenerative changes. The author quite appropriately points out that the paranasal sinuses are "air-bearing" cavities and as such ventilation and not lavage should be the object of any surgical intervention in inflammatory processes. Wisely does he observe that with intelligent management most cases of sinusitis tend to recover.

RADIOLOGY

UNDER THE CHARGE OF

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Present Status of Hysterosalpingography.—WITWER, CUSHMAN and LEUCUTIA (*Am. J. Roent. and Rad. Therap.*, 1930, **23**, 125) regard hysterosalpingography by means of lipiodol as a safe and simple procedure. In a series of 512 cases the only accident observed was that of a ruptured tube which led to no ill effects. The method is of great diagnostic value in developmental anomalies of the genital organs, in tubal affections leading to sterility, in certain very carefully selected cases of pregnancy in which therapeutic abortion is indicated or when a differential diagnosis from other obscure conditions is essential, in uterine tumors, excepting malignancies, and in certain extrauterine tumors. The contraindications are recent hemorrhage, inflammatory conditions that are not completely quiescent, active infections or malignancies involving the cervix, previous intrauterine interventions, ectopic gestation or uterine gestation in which a therapeutic abortion is not desired, infected cervical or uterine polyps and fever. In certain instances the injection of lipiodol is of direct therapeutic value.

Intravenous Method of Cholecystography.—In the experience of WATERS and KING (*Am. J. Roent. and Rad. Therap.*, 1930, **23**, 34) with the intravenous injection of phenoltetraiodophthalein, the dye is comparatively nontoxic, for a few disagreeable reactions were encountered and none of these was alarming. The method of injecting the dye is not technically difficult nor unusually time-consuming, three injections being easily given in one hour. The cholecystograms are far superior to those obtained following the oral administration and the information gained from the films is more conclusive, because the intravenous administration insures the introduction of a definite amount of dye and is not complicated by factors of solution and absorption in the gastrointestinal tract. In addition, the liver function can be simultaneously determined.

Factors Determining Radioresistance in Tumors.—EWING (*Radiology*, 1930, **14**, 186) holds that resistance of tumors to irradiation may be due to the adult character of the stroma; this form of resistance is observed in many types of sarcoma of bone, nerve and cartilage. The adult characters of epithelial cells and the substantial blood supply render adenomas and papillomas radioresistant. Carcinomas are resistant in inverse ratio to the degree of anaplasia and in direct proportion to the amount of desmoplastic reaction which they excite. In mixed

tumors in which one element is sensitive and the other resistant, the malignant portion may be sterilized, although the tumor does not diminish in size and a false impression of radioresistance may be gained; This is exemplified in mixed tumors of the testis and teratomatous tumors in the abdomen, kidney or sacral region. A special instance of spurious resistance is seen in very vascular giant-cell tumors, which are well designated as benign bone aneurysms. The nature of the tumor bed may favor or retard response to treatment; the high resistance of malignant tumors invading bone or cartilage is well known. Infected tumors which are the seat of exudative inflammation do not react well to treatment, but a full explanation of this fact is hard to find.

Roentgen Irradiation in Unresolved Pneumonia.—The suggestion is offered by MERRITT and MCPEAK (*Am. J. Roent. and Rad. Therap.*, 1930 **23**, 45) that irradiation should be instituted in all cases of pneumonia showing definite Roentgen signs of delayed resolution three weeks after the onset. Of 7 cases thus treated by the authors, 4 cleared up entirely, 2 improved definitely and 1 was unchanged.

Advantages and Limitations of External Radiation in the Treatment of Rectal Cancer.—External radiation, in the opinion of BINKLEY (*Radiology*, 1930, **14**, 207), constitutes the first step in radiation therapy of all rectal cancers, and in certain cases may be the only form of treatment necessary. The effect is limited by the depth of the tumor, the tolerance of the skin and the radioresistance of the cancer. External radium radiation is more effectual than high-voltage Roentgen rays. The two types of radiation may be combined advantageously.

Treatment of Malignant Growths of the Nasal Accessory Sinuses and Nasopharynx.—Radium and Roentgen rays are of value in treating this group of cases, according to QUICK (*Radiology*, 1930, **14**, 191), but, except in palliative procedures, must be used in conjunction with surgery. Radium and Roentgen rays may be depended upon to eradicate the tumor tissue if applied accurately and uniformly throughout the growth in sufficient dosage. Surgery must be employed to provide exposure for radium application and adequate drainage. The anatomic relations are such that infection is a much greater menace here than in newgrowths in most other locations.

Treatment of Malignant Tumors of the Eye and Orbit by Radiation.—The present status of radiation therapy for tumors of the orbit is summarized by RODENBAUGH (*Radiology*, 1930, **14**, 309) as follows: In tumors of the conjunctiva and cornea, radiation, preferably from radium, with a maximum conservation of normal tissue looking to clinical cure should be given first consideration. In basal-cell epitheliomas of the adnexa, as elsewhere in the body, the clinical cures are satisfactory and radiation is superior to other methods of treatment. The angiomas, lymphomas, sarcomas, granulomas, fibromas and nevi, occurring as primary tumors, are susceptible to radiation, their response varying with their histologic structure. The numerous metastatic tumors will vary in their response to radiation, their susceptibility depending on their histologic structure. Types of localized tumors of

the iris or ciliary body, of doubtful nature, have been favorably influenced by radiation, and such treatment should receive consideration before resorting to radical surgical methods. It is of greater importance to secure clinical regression of a newgrowth, with conservation of essential structures, than to have a histologic study, with loss of function.

Roentgen Diagnosis and Treatment of Thymomata.—In the view of DAUB (*Radiology*, 1930, **14**, 267) too large a percentage of primary tumors of the thymus have passed unrecognized before autopsy. While the cases are uncommon they are not as rare as has been thought. The sarcomatous type of tumor predominates but a carcinomatous type of tumor also occurs. Roentgenologic examination of the chest will reveal the tumor as a more or less circular, sharply defined, nonpulsating mass occupying the anterior mediastinum. Roentgen ray therapy is indicated as soon as the diagnosis is made; the tumors are quite sensitive to radiation therapy and their prompt regression can usually be expected.

Results Obtained in the Treatment of Carcinoma of the Cervix Uteri With Radium and Roentgen Rays.—Reviewing 1094 patients treated during the decade from 1915 to 1924 inclusive, of whom 1001 were traced, BOWING and FRICKE (*Radiology*, 1930, **14**, 211) find that in the small operable group, operated on and subsequently treated by irradiation, 75 per cent survived five years. Of the borderline cases, 61.53 per cent lived five years. In the inoperative group, 21.49 per cent of the patients were living after five years, and in a group previously treated elsewhere there were 24.82 per cent five-year survivals.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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Brown-Sequard Paralysis.—HASSIN, KENDRICK and CONNELLY (*J. Nerv. and Ment. Dis.*, 1930, **72**, 245) present 2 cases, 1 occurring in a patient with syphilis, and one in a patient with poliomyelitis. The poliomyelitis case showed a motor paralysis of the left upper extremity with contralateral anesthesia. The sensory disturbance appeared in the form of syringomyelic dissociation and involved the entire right side of the body up to the level of the seventh cervical vertebra. He considers that this syndrome was caused by interruption of the long fibers of the spinothalamic tract. The case with syphilis exhibited paralysis of the left leg with disturbances of position sense, col-

lateral analgesia and thermoanesthesia up to the level of the sixth thoracic segment. Antiluetic treatment brought no relief and operation was resorted to, at which fibrous tissue was found over the dura at the level of the sixth and seventh thoracic segments (pacyhmeningitic in type). Following this there was remarkable improvement. The author discusses the prognosis in the second type of case and the advisbility of operative procedure in those luetic cases which do not respond to chemotherapy, and so forth.

Psychologic Study of Accident Proneness.—FARMER (*Personnel Journal*, 1930, **2**, 115) reports a study of accident proneness in relation to intelligence and sensory motor equipment. He finds a positive relation in that the 25 per cent of the subjects making the poorest scores showed an accident rate 2.5 times greater than that of the remaining 75 per cent. Also the accident rate of these subjects tended to increase with experience rather than diminish, as did the other groups. The same tests showed a similar relation to industrial proficiency, hence the author contends that the utilization of such tests for the selection of employees would increase efficiency in two directions: by decreasing accidents, and by the acquiring of more efficient workers.

The Prevention of Mental Deficiency by Sexual Sterilization.—ROBIE (*Psychiat. Quart.*, 1930, **4**, 474) records a group of case studies indicating hereditary tendencies in mental deficiency, and discusses the possibilities of social control of this problem by means of segregation and sterilization, and concludes that sterilization offers a better mode of approach since segregation involves the housing of so many individuals that it is impracticable from a social and economic point of view. Since the sterilization operation in males is very simple, and the new method of sterilizing the female by intrauterine cauterization of the uteris and the Fallopian tube through a hysteroscope, previous objections to the operative procedures are fairly well met. He believes that the constant carrying out of such a program would decrease the number of mental defectives as well as the amount of poverty, state dependency, prostitution, venereal disease and delinquency. He advocates the passing of sterilization laws in all states to permit the sterilization of mental defectives in state institutions as well as in selected cases outside of institutions.

A Clinical and Pathologic Study of Three Cases of Epidemic Encephalitis.—POOL (*J. Neurol. and Psychopathol.*, 1930, **11**, 45) presents 3 cases in detail and attempts to correlate the clinical features and the pathologic findings. He argues that the only adequate explanation of the outstanding symptoms which constitute Parkinsonism is that of sympathetic decontrol due to interference with fibers of the rubrospinal tracts; that the symptoms of palilalia and sialorrhœa are probably the result of irritative phenomena due to degenerative products; and that the type of inflammatory cell encountered suggests that the disease is a manifestation of a chronic progressive encephalitis rather than a sequel to an acute infection. His argument is based on the comparison of the clinical pictures of Parkinsonism and lesions of the pyramidal tracts.

Psychosis Associated With Myxedema.—ZIEGLER (*J. Neurol. and Psychopathol.*, 1930, **11**, 20) gives a fairly adequate review of cases of myxedema previously reported with mental symptoms, and reports 3 cases of his own. He considers that thyroid deficiency brings about a physiologic depression, which may precede abnormal mental states. On the whole, he believes the latter to conform more or less to the personality reaction of the individual patient rather than to follow any fixed clinical picture of mental disease. He finds great variation in the types of psychiatric manifestations. All of his patients improved on the administration of desiccated thyroid gland.

Biologic and Serologic Methods of Diagnosis in Epilepsy.—DE THURZO (*J. Neurol. and Psychopathol.*, 1930, **11**, 36) reports in some detail a series of experiments in humoropathologic reactions in epilepsy. One of the more interesting findings resulted from an application to dementia præcox of a test for immune-hemolysin formation in inoculated animals. This reaction he calls "positive pleohemolytic reaction" and finds the highest titer occurring in dementia precox when compared with other mental patients and healthy subjects. Applying a similar technique to epilepsy, convulsions were obtained in less than one minute, in 6 cases, after intravenous injections of 3 to 4 cc. of blood serum. In other cases intraperitoneal inoculation of blood serum was used and seizures did not occur but the body weight notably decreased. These findings substantiate those of Pagniez, Mouzon and Turpin. Blood serum warmed for ten minutes at 58° C. loses its toxic power. He finds slight changes in the bicolored mastic reaction, in the form of slightly irregular curves, and for this reason believes this reaction to be the most precise of all the colloid tests. In addition he has devised a China ink reaction of spinal fluid, rather simply carried out, which he finds positive in 87 per cent of the cases of epilepsy. The results of various reactions are published in the table accompanying the article.

PATHOLOGY AND BACTERIOLOGY

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The Growth of Endometrial Autotransplants in the Rabbit.—Following the work of Sampson (1921) and Jacobson (1922) a great deal of interest has been given to the theory that portions of endometrium may become implanted upon the peritoneal surface. It has been generally accepted that in the human these transplants arise through the regurgitation of menstrual fluid through the Fallopian tubes. Several authors have undertaken the experimental reproduction of

endometrial implantation in lower animals. GLEAVE (*J. Path. Bact.*, 1930, **33**, 675) found that the implantation of endometrium occurred with considerable ease in the rabbit. At times, however, adhesions formed at the site of implantation and multiocular or unilocular cysts of some size occupied the site. Ordinarily, however, the endometrial implants resembled the endometrium of the uterus of the same animal. Further, the endometrial changes observed in the uterine cycle were also to be observed in the implants. It was also noted that the endometrial implants were influenced by the ovarian hormone, estrin, in a manner similar to the uterine endometrium.

HYGIENE AND PUBLIC HEALTH

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Will the Inhalation of Siliceous Dusts Activate a Partially Healed Focus of Tuberculous Infection?—GARDNER (*U. S. Pub. Health Rep.*, 1930, **45**, 282) notes that it is usually thought that tuberculosis in cases of pneumokoniosis is an occupational infection; he believes, however, that the infection has occurred in the case of granite cutters prior to exposure to dust. The present study was made on guinea pigs which were infected by inhalation of a low virulence culture. This culture, used in this manner, produces a disease that tends to recovery. When exposed for prolonged periods to siliceous dusts the tendency to healing is lost and a distinctly progressive quality is observed in the lesions. The spread seems to be both by the air passages and through the blood stream—evidence of the latter being seen in the involvement of abdominal viscera. Microscopic examination confirms the adverse influence of the dust. The author admits that it is not at present desirable to carry the results on guinea pigs over to human pathology.

The Immunologic Significance of Colostrum.—SMITH (*J. Exper. Med.*, 1930, **51**, 473) declares that the protective antibody content of normal cow serum is below that of colostrum of the same animal. The method used does not permit the titration of the actual amount of the antibody in serum. Quantities up to 2 cc. have no protective effect. The same limitations apply to the titration of milk owing to the introduction of large quantities of foreign protein into the peritoneal cavity of the guinea pig. When cows were immunized and a serum of high titer obtained, the antibodies in the milk of such cows rose to within the range of the method of testing. The relation of the protective capac-

ity of serum to that of milk was approximately 1 to 120 and 1 to 40 in the two animals. These figures do not differ much from those obtained by early investigators titrating the antitoxic content of serum and milk of animals undergoing immunization with diphtheria toxin. In the two experiments on calves, two and a quarter and eighteen days old respectively, fed a highly protective serum, no increase in agglutinins or protective antibodies could be demonstrated. The postponement of colostrum to the twelfth and eighteenth hour, respectively, did not prevent normal growth. SMITH and LITTLE (*ibid.*, 483) continuing these studies, under certain safeguards, such as isolation, raised calves from a large dairy herd by feeding normal and immune cow serum in place of colostrum. The losses were about 1 out of 10 in the later experiments. This outcome may probably be improved by the subcutaneous injection of serum during the first day. This loss may be no greater than that under ordinary conditions, since sporadic deaths among calves are not infrequent. However, no satisfactory statistics are available for comparison with results as given above.

The Extent of Gonorrhea and Syphilis in the United States.—A series of prevalence studies has been carried out in communities with a total population of more than 17,758,000 located in various parts of the United States, and representative of the population as a whole. It is estimated that there are in the whole country 643,000 cases of syphilis and 474,000 cases of gonorrhea constantly under medical care. Twenty-one per cent of the cases of gonorrhea and 40 per cent of the cases of syphilis are treated in public clinics. The combined case rate for gonorrhea and syphilis for the male population was nearly twice as high as that of the female, the rates being 9.65 and 4.85 per thousand, respectively. This difference was more pronounced for gonorrhea than for syphilis. Venereal diseases as a group far outnumber all other reported infections except influenza in times of an epidemic. The experience in the military forces of this and other countries in peace and in war time shows the venereal diseases to exceed any other condition as a cause of noneffectiveness. Among the second million men drafted during the World War, 56.7 per thousand were found by a casual clinical examination to have a venereal disease. It is estimated that in the continental United States there are 423,000 new cases of syphilis which seek treatment during the early stage (the first year) of the disease, and likewise, 679,000 new cases of gonorrhea each year which come under medical care during the first three months of the infection. This incidence represents an annual attack rate per 1000 population of 3.46 for syphilis and 5.71 for gonorrhea. PARRAN and USILTON (*J. Soc. Hyg.*, 1930, **16**, 31), estimating 643,000 cases of syphilis and 474,000 cases of gonorrhea constantly under medical care in the United States, give case rates for gonorrhea 4.88 for males and 1.78 for females; and for syphilis 4.77 for males and 3.08 for females. Approximately 31 per cent of the total cases of venereal diseases under treatment are found among presumably indigent persons, inasmuch as this percentage of total cases were being treated at public expense in clinics, hospitals or other institutions. The peak-age group for the onset of both gonorrhea and syphilis has been determined as twenty to twenty-five years. A greater prevalence of venereal disease exists among the Negroes than

among the white population, the rate per 1000 being 8 for white and 11 for colored population. A recent study of the rural Negro in a southern state indicated that as high as 24 per cent of the entire population of more than one year of age showed a positive Wassermann reaction. The results of a number of published reports over a ten-year period indicated that of women admitted to maternity hospitals 6.9 per cent had a positive Wassermann reaction. General paralysis contributes 4 per cent of the population of our insane institutions. Syphilis stands first or second among the most frequently reported infections to the Public Health Service from the several state health departments. Gonorrhea stands about fifth. Among the general male population between the ages of fifteen and forty-five years it is estimated that the number of noneffective days lost through venereal diseases would approximate 21,000,000 days per annum, or a loss of approximately a half a day for each male of the United States between the ages of fifteen and forty-five years.

The Type Distribution of Meningococci in the United States During 1928 and 1929.—BRANHAM, TAFT and CARLIN (*U. S. Pub. Health Rep.*, 1930, **45**, 1131) note that in 1928 and 1929 epidemic meningitis was more prevalent than at any other time since the World War, that it was highly fatal—50 per cent death rate and over in some localities—and that serum therapy was disappointing in results. The authors sought to determine whether the organisms differed from those found in earlier years. It was found that generally speaking 90 per cent of the cultures agreed with those found in earlier years, while 10 per cent were atypical.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF OCTOBER 20, 1930

Preparation and Properties of Crystallized Alkali Salts of l-Cystine.—GERRIT TOENNIES and THEODORE F. LAVINE (from the Research Institute of the Lankenau Hospital, Philadelphia). l-Cystine, while insoluble in water, forms soluble salts with mineral acids and with alkali hydroxides. A method for the isolation of the alkali salts in crystallized form was found, consisting in treating cystine with a little less than the equivalent amount of alkali in methyl alcohol or in a mixture of water and ethyl alcohol, the composition being different according to the alkali (lithium, sodium or potassium) used, filtering from excess cystine, immediately precipitating by several volumes of acetonitrile or of a mixture of acetonitrile and ether, and allowing to stand for several hours before filtering. The sodium salt crystallizes with one molecule of water of crystallization. The potassium, as well as the

lithium salt, was observed in two different crystal forms. The specific rotation of cystine in solutions of its alkali salts is less than half as large as in an acid solution of the same concentration. However, by comparing acid solutions prepared from a salt and from free cystine, under equal conditions, practically identical values are obtained, proving that the substances described are simple salts from which the original cystine can be recovered unchanged. All three salts are very soluble in water; the solubilities in methyl and ethyl alcohol were determined quantitatively. The solubility in methyl is considerably larger than that in ethyl alcohol for all three salts. The solubility in the alcohols is largest for the potassium salt, less for the sodium, and smallest for the lithium salt. While aqueous solutions are stable for a number of days, the solutions in methyl alcohol begin to decompose, with formation of ammonia, almost immediately. The specific rotation of methyl-alcoholic solutions is almost three times as large as that of aqueous solutions. The solubility relations as well as the differences in stability and optical rotation between aqueous and alcoholic solutions suggest that the undissociated salt molecule is predominant in the alcoholic solutions.

Initial and Recovery Heat Production of Nerve.—D. W. BRONK (from the Johnson Foundation for Medical Physics, University of Pennsylvania). Employing recent improvements in thermopile and galvanometer design the course of the heat production of frog's nerve has been determined. Exceedingly accurate analyses have been obtained of the heat production resulting from nine to fifteen seconds stimuli showing a progressive increase in the rate of heat production during the period of stimulation. This is the sum of the heat associated with the conduction process and that accompanying the recovery therefrom. The recovery heat production is at a maximum rate immediately after the end of the stimulation and continues for some minutes at a decreasing rate. The duration of this recovery phase is largely dependent upon the temperature. At 19° C. it is about eleven minutes and at 24° C. about seven and three-quarters minutes. Seven experiments, comprising about seventy individual determinations, give the initial heat production as 8.9 per cent of the total. This is compared with the previous determinations by DOWNING, GERARD and HILL (*Proc. Roy. Soc. Biol.*, 1926, **100**, 223) and GERARD (*J. Physiol.*, 1927, **62**, 349) of about 11 per cent for frog's nerve and HILL's (*Proc. Roy. Soc. Biol.*, 1929, **105**, 153) recent value of 2.25 per cent for crustacean nerve.

A Study of Mammalian Fetal Movements, with Special Reference to the Influence of Narcotics.—ENGELBREKT A. SWENSON (from the Department of Anatomy, University of Pennsylvania). In all my previous studies on mammalian fetal movements it has been necessary for me to employ small amounts of narcotics. These drugs, when given in doses large enough to quiet the mother animal, either completely suppress or modify the muscular movements of the embryo or fetus. For these reasons they are not desirable.

Recently we have perfected a method which permits one to observe fetal movements in rats and guinea-pigs, for much longer periods of time than heretofore, and without using drugs to anesthetize the

mother. The new method consists of the production of anesthesia by cerebral compression, and is carried out as follows:

The skin and underlying tissue immediately over the occipital protuberance of the mother rat or guinea-pig are frozen with carbon dioxid ice. Through an incision made in this frozen tissue a small hole is made in the skull by means of a dental engine and burr. The degree of compression of the brain sufficient to produce general anesthesia is readily accomplished by inserting a small plug of absorbent cotton through the opening and gently forcing it into the space between the skull and the intact dura.

There is no indication of spinal shock and very little, if any, evidence of surgical shock in the mother. The quietness and composure of the mother permit of uninterrupted observation of the embryos or fetuses throughout the experiment. The mother and the young seem to suffer less from this procedure than from any other methods used heretofore. The effect of narcotics upon the embryo or fetus have been entirely eliminated.

Using as a norm the types and extent of fetal movements as observed in preparations in which the mother is thus anesthetized without drugs, it is now possible to study accurately the effects of drugs upon the active muscular movements of the embryo or fetus. Ether and chloroform, when given in exceedingly small doses to the mother, tend to increase the spontaneous movements of the fetuses. Cocain and novocain partially suppress some fetal movements, even when given as local anesthetics to the mother. Subcutaneous injections of magnesium sulphate into the mother, in doses large enough to quiet her, generally suppress all fetal movements. Sodium amytal, however, when given in doses large enough to completely anesthetize the mother, characteristically alters but does not completely suppress all muscular movements of the fetuses.

The study and analysis of the fetal movements have been made both by direct observation and with the aid of the moving-picture apparatus.

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